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THE TREATMENT OF HEADACHE

With Particular Reference to the Use of Cafergone (Ergotamine Tartrate and Caffeine) for the Relief of Attacks

FRENCH K. HANSEL, M.D., F.A.C.A.
St. Louis, Missouri

HEADACHE is the most common symptomatic ailment encountered in office practice. Head pain, from the most severe to the mildest type, is almost always of a functional nature and is rarely caused by organic disease. Those who are subject to the milder types do not often seek medical aid, either because the discomfort is not incapacitating, or because relief is quickly obtained with one of the readily available coal tar products. The consideration and inquiry about headache in the general medical history will reveal its occurrence, at least in the milder forms and as a secondary complaint, in a large percentage of all patients. Not infrequently, however, a history of attacks of severe headache may be revealed as a complaint entirely unrelated to the chief complaint. In many of these instances, the patient has already exhausted every means of obtaining satisfactory relief.

TYPES OF HEADACHE

Up to the past few years, almost all of the severe types of functional headache were classified as typical or atypical migraine. These represent the incapacitating forms in which the patient suffers the most pronounced agony and in which vascular mechanisms have been shown to play an important role. Considering this group as a whole, the incidence of true classical migraine is considerably less than that of the atypical type. Until only a few years ago, most of the atypical types remained in an unclassified group. With the recognition of allergy as the cause for many functional disturbances, a small percentage of them could be classified in this

The Sandoz Chemical Works, Inc., supplied the preparation used for this investigation, which was formerly known under clinical investigation as E.C. 110.
Dr. Hansel is Director of the Hansel Foundation.

category. Vaughan was the first observer to report a large series of cases of this type. He used the term "allergic migraine" which should be "allergic headache."

In 1939 Horton, MacLean and Craig reported a new syndrome of vascular headache, and in 1941 Horton presented a large group of these cases which he designated as "histaminic cephalalgia." Since that time, we have applied the principles of diagnosis and treatment suggested by Horton and have found that a very high percentage of the unclassified headaches fall into this group. A still larger number of cases closely related to this type may be considered as "atypical histaminic cephalalgia."

For all practical purposes, the majority of cases of non-organic headache may be classified as (1) migraine, (2) atypical migraine, (3) tension headache, (4) histaminic cephalalgia, (5) atypical histaminic cephalalgia, and (6) miscellaneous.

Migraine.—Wolff, von Storch and Horton define the syndrome of migraine as characterized by the following five factors: (1) periodicity, (2) cephalalgia, (3) gastrointestinal dysfunction, (4) cortical disturbance, (5) a familial history of migraine.

Atypical Migraine.—Periodic cephalalgia associated with any one of the latter three factors listed above.

Histaminic Cephalalgia.—According to Horton, "histaminic cephalalgia is characterized by a unilateral headache which usually begins in the latter decades of life, is of short duration, as it generally lasts less than an hour, commences and often terminates suddenly, tends to awaken the patient at night one to two hours after he has gone to sleep and is frequently eased by the patient sitting up or standing erect. It is associated with profuse watering and congestion of the eye, rhinorrhea or stuffiness of the nostril, increased surface temperature and, often, swelling of the temporal vessels on the involved side of the head. Pain is the outstanding complaint. It is constant, excruciating, burning and boring; it involves the eye, the temple, the neck and often the face."

Atypical Histaminic Cephalalgia.—We have also observed a large group of cases, somewhat more common than the typical ones which present most, but not all, of the characteristics of the typical type. They may lack the sweating and tearing phenomena, may be of longer duration, may not begin or end suddenly, or deviate from the typical in some other features. As a rule, the pain is not as severe, consequently the extent of the vasodilatation is less.

Tension Headaches.—This type of headache is associated with nervous tension or a state of physiologic hypertonicity, which is followed by hypotonicity and subsequent vasodilation in which state the headache occurs.

The headache may be localized or generalized and may involve any one or more vascular areas. A certain degree of nervous tension is frequently associated with the migraine syndrome.

Miscellaneous Unclassified Headaches.—This constitutes a very large group of patients in whom the headache may vary from the severe to the mildest type. They may simulate any of the above mentioned types, but lack distinct features by means of which they may be classified. As will be pointed out later, they present features of vascular involvement and respond to the same types of therapy.

MECHANISM OF VASCULAR PHENOMENA IN VARIOUS TYPES OF HEADACHE

Wolff and his associates have shown that in migraine the pain is vascular in origin and that there are three phases to consider:

1. *The Vasoconstrictor Phase.*—This causes the scotomas and cortical manifestations. Pain does not occur in this phase of vasoconstriction. A vasodilatory agent may abort an attack at this time.

2. *Vasodilator Phase.*—The vasodilation is the immediate cause of the pain, in that pain-sensitive structures surrounding certain vessels are stretched and pulled. Vasoconstrictor agents, such as ergotamine tartrate (Gynergen) or dihydroergotamine methanesulfonate (D.H.E. 45), if administered early by injection, will abort the attack in the majority of instances.

3. *The Edema Phase.*—This will follow if the vasodilation lasts for any considerable length of time and is comparatively resistant to vasoconstrictor therapy.

In migraine the initial vasoconstrictor phase ends in vascular fatigue, producing the state of vasodilation, which becomes increasingly difficult to relieve by vasoconstrictor agents once it has completely developed. This is also true in the tension headache. Practically all the other types of headache apparently do not have a definitely perceptible prevasoconstrictor phase so that the headache begins suddenly with vasodilation. Vasoconstrictor agents are, therefore, the most effective symptomatic treatment for this type.

THE TREATMENT OF HEADACHE

In the management of all types of headache, every possible attempt should be made to eliminate or correct the primary cause of the attacks. This is sometimes possible and the patient needs no further treatment. The elimination of allergic headache by the removal or avoidance of the offending allergen is an example of such management. In the cases of histaminic cephalalgia, the patient may be relieved of headache for an

indefinite period after adequate histamine therapy. Recurrence of attacks, however, is the rule. In some instances, treatment must be continued indefinitely. In a group of fifty-one patients with typical histaminic cephalalgia who were treated with histamine by Horton, forty-eight had complete relief of attacks for varying periods of time. Among twelve atypical cases, four patients were completely relieved at the time of dismissal. The other eight patients had 50 to 90 per cent relief, but had recurrences of lesser degree. We have had somewhat similar results with the use of histamine in such cases.

THE TREATMENT OF MIGRAINE WITH HISTAMINE

In a recent report, Macy and Horton presented their observations on the treatment of 144 migrainous patients with histamine. Seventy to 85 per cent of patients with typical migraine and 75 to 100 per cent of patients with atypical migraine showed significant improvement during the period of treatment with combined intravenous and subcutaneous therapy, which was considered the method of choice. Macy and Horton concluded that although histamine was not found to be either a specific or truly curative agent in the migraine syndrome, until such an agent is found, histamine will continue to have a place among prophylactic measures of value in the clinical management of the migrainous patient.

THE TREATMENT OF ATTACKS OF MIGRAINE WITH ERGOTAMINE TARTRATE AND ITS DERIVATIVES

Since no specific medicinal cure has been developed for migraine, the only hope for the present is some effective means of aborting the attacks. So far, it is generally agreed upon that ergotamine tartrate (Gynergen) and dihydroergotamine methanesulfonate (D.H.E. 45) are definitely superior to all other drugs for this purpose. These findings have been more recently confirmed by Friedman and Brenner in a group of ninety-four patients. Among 161 trials with ergotamine tartrate (Gynergen) and dihydroergotamine methanesulfonate (D.H.E. 45), they reported good relief in 53 per cent, fair relief in 20 per cent and no relief in 27 per cent. Vasodilators and analgesics were of little value in comparison. It was emphasized that in using ergotamine tartrate (Gynergen) or dihydroergotamine methanesulfonate (D.H.E. 45), it is important, if the best result is to be obtained, that an adequate dose, preferably by subcutaneous injection, be administered early in the attack. Friedman and Brenner observed that combinations of ergotamine tartrate (1 mg.) with caffeine (100 mg.) by mouth, or ergotamine tartrate (2 mg.) and atropine (0.4 mg.) in form of rectal inserts, proved more effective in relieving attacks of migraine than either ergotamine tartrate or dihydroergotamine methanesulfonate alone by the oral route.

Satisfactory results in the treatment of attacks of migraine with ergot-

amine tartrate (1 mg.) and caffeine (100 mg.) (Cafergone) were also reported by Horton, Ryan and Reynolds. Among twenty-five patients excellent results were obtained in sixteen, good results in six and poor results in three. Side effects were noted in only one instance. Practically all the patients had previously used ergotamine tartrate alone by mouth but found that Cafergone was uniformly more effective. The average dose was two tablets administered at the onset of an attack.

THE TREATMENT OF MIGRAINE AS WELL AS OTHER TYPES OF HEADACHE WITH CAFERGONE (ERGOTAMINE TARTRATE 1 MG. AND CAFFEINE 100 MG.)

In a group of eighty-four patients with various types of headache, Cafergone was administered for the relief of attacks. The results are shown in Table I.

TABLE I. RESULTS OF TREATMENT WITH CAFERGONE

		Excellent	Good	Poor
Group I				
Migraine	6	3	2	1
Tension	14	3	4	7
	20	6 30%	6 30%	8 40%
Group II				
Histaminic Cephalalgia	26	24	1	1
Atypical Histaminic Cephalalgia	18	12	4	2
	44	36 81.8%	5 11.4%	3 6.8%
Group III				
Miscellaneous				
Facial Pain	2		2	
Ocular Pain	1	1		
Post Trauma	2	1		1
Otalgia	1	1		
Vertigo	1	1		
Parotid	1	1		
Laryngeal	2		2	
Unclassified	10	7	3	
	20	12 60%	7 35%	1 5%
Total, Group II & III	64	48 75%	12 18.75%	4 6.25%
Total, All Groups	84	54 64.3%	18 21.4%	12 14.3%

The average dose necessary for relief was two tablets. The milder attacks were often relieved with one tablet. The patient was instructed to take not more than three tablets, for it was observed that more than this number did not appear to give additional relief. The patient was also instructed not to take these doses repeatedly. By following this plan, toxic side effects were entirely avoided. In only three instances did any side effects, such as nausea and epigastric distress, occur. Since nausea and vomiting are frequent occurrences in the course of the migraine attack, the importance of taking the tablets as early as possible is obvious. In all instances, the effectiveness of the tablets was evaluated on the basis of several trials.

Although Cafergone was developed primarily for the relief of the migraine attack, a review of the results recorded in Table I shows that it is even more effective and has a wider range of usefulness in the relief of attacks of other types of headache.

Considering the fundamental mechanism of the production of headache, it is apparent, as Horton and others have pointed out, that pain occurs in the phase of vasodilation. In migraine and tension headache, there is a definite vasoconstrictor phase which precedes the vasodilatation. In other types of headache, the vasoconstrictor phase is usually absent or, at least, insignificant. The slow onset of attacks not infrequently noted in atypical histaminic cephalalgia and in the miscellaneous group suggests, however, that some degree of preliminary vasoconstriction may occur. In Table I it is apparent that much better results with the drug are obtained in those cases in which the preliminary vasoconstrictor phase does not manifest itself. Prolonged vasoconstriction apparently results in vascular fatigue, and when vasodilation develops, it is sometimes difficult to reproduce the degree of vasoconstriction which is necessary to relieve the attack.

In the cases of typical histaminic cephalalgia, and to a lesser degree in the atypical group, the onset of the attack with vasodilation is sudden, unpreceded apparently by vasoconstriction and with absence of vascular fatigue—hence the prompt and satisfactory relief obtained with Cafergone in a very high percentage of cases.

Upon consideration of all these factors, the results may be more accurately evaluated by dividing the cases into three groups as follows: (1) the migraine-tension, (2) the histaminic cephalalgias, and (3) the miscellaneous. It is apparent that the poorest results in our series were obtained in the migraine and tension cases. In group two, excellent results were noted in twenty-four of twenty-six cases of typical histaminic cephalalgia. In the atypical cases, the results were highly satisfactory, but to a lesser degree than in the aforementioned group. In the miscellaneous group, which includes unclassified cases, excellent results were noted in 60 per cent.

In conclusion, it should be emphasized that the oral administration of Cafergone possesses the advantage of high degree of effectiveness and ready availability to the patient when needed. However, we have noted that on many occasions when the injectable preparations of ergotamine tartrate (Gynergen) and dihydroergotamine methanesulfonate (D.H.E. 45) could be administered at the onset or even during an attack of migraine or other types of severe headache, they were more effective and prompt in action.

SUMMARY

1. Cafergone, a combination of ergotamine tartrate (1 mg.) with caffeine (100 mg.) for oral administration, is superior to ergotamine tartrate alone. The presence of caffeine reduces considerably the dose of ergotamine otherwise required for the relief of headache.

2. Although Cafergone was developed primarily for the relief of the migraine attack, it is uniformly effective and has a much wider range of usefulness in the relief of attacks of headache of all other types, especially typical and atypical histaminic cephalalgia.

3. The administration of ergotamine tartrate (Gynergen) or dihydroergotamine methanesulfonate (D.H.E. 45) by subcutaneous injection is more reliable than Cafergone, especially for the relief of the migraine attack, tension or other types of severe headache if it can be given at the onset or even during the episode.

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634 North Grand Blvd.

THE NEW YORK ALLERGY SOCIETY

Just before going to press, The New York Allergy Society, whose meeting is announced in the News Items, sent in the following program which will be presented Wednesday, May 4, 1949, at 8:30 p.m. in Room 440 of the New York Academy of Medicine.

CASE PRESENTATIONS

1. Report of Death in a Four and One-Half Year Asthmatic Child—Drs. Louis J. Schloss and Robert Chobot, University Hospital, New York University-Bellevue.

2. A Case of Co-Existent Insulin Allergy and Insulin Resistance—Dr. William B. Sherman, Presbyterian Hospital.

3. Clinical and Experimental Studies of Insulin Allergy and Resistance—Dr. Francis C. Lowell, Boston, Massachusetts.

4. An Unusual Case of Severe Eczema Solare—Dr. Maury D. Sanger, Brooklyn Regional Office, Veterans Administration.

5. Atmospheric Mold Survey of the New York Metropolitan Area for 1948—Dr. David Merksamer, Jewish Hospital, Brooklyn, New York.

6. An Unusual Case of Periarteritis Nodosa with Recovery—Dr. Frederic P. McIntyre, Flower-Fifth Avenue Hospital.

IMMEDIATE URTICARIAL REACTIONS TO INTRADERMAL INJECTIONS OF BACTERIAL ANTIGENS

Preliminary Report

BENNETT KRAFT, M.D., F.A.C.A., MARK H. MOTHERSILL, M.D., F.A.C.A., and R. H. NESTMANN, M.D.
Indianapolis, Indiana

AN examination of the standard textbooks on allergy indicates a belief on the part of many of the authors that immediate skin reactions to bacterial antigens occur but rarely. The possibility that this rarity might be explained by denaturation of the bacterial antigen during its preparation has been mentioned by Vaughan,[3] Wells,[5] and Zinsser.[6] Wells has reported that when heat-killed tubercle bacilli were injected into *tuberculous* guinea pigs, the tuberculin type skin reaction was obtained, but that injection of *ground* tubercle bacilli in such guinea pigs elicited an *immediate* wheal reaction. Since a supply of "undenatured bacterial antigens"* was available, it was decided to perform a series of tests in order to determine the frequency with which immediate reactions might result.

MATERIALS AND METHODS

The antigens used in these series of tests were prepared by the Krueger method[2] of rendering bacteria nonviable by mechanical disruption in a ball mill and removing residual live cells by ultrafiltration. By this means the antigen preparation becomes sterile without the application of heat or chemicals. Seven bacterial antigens prepared, respectively, from staphylococci, M. catarrhalis, pneumococci, streptococci, E. coli, H. influenzae, and Friedlander's bacillus were used. Each of the antigen preparations was diluted to the point where it was calculated to represent 0.01 mg. of nitrogen per cubic centimeter.

Intradermal skin tests were made on 200 patients, each of whom had an allergic history. One hundred of these were seen in private practice, the second hundred in the Outpatient Allergy Clinic of the Indianapolis General Hospital. Subsequently, as a control series, 100 patients with nonallergic histories were skin tested at the Indianapolis General Hospital with the three bacterial antigens which gave the highest percentages of immediate reactions in the allergic patients. The three antigens were staphylococcus, M. catarrhalis, and pneumococcus. Each of the control patients was questioned in regard to the possibility of a personal or family history of allergy and was not used unless both were negative.

In each instance, the seven antigens were injected intradermally into the arm of the subject, and an eighth injection, consisting of physiological saline, was used as a control. The injection sites were observed twenty to thirty minutes later. Borderline reactions were recorded as negative.

*Supplied by Eli Lilly & Company.

TABLE I. SUMMARY OF POSITIVE INTRADERMAL SKIN TESTS WITH BACTERIAL ANTIGENS

Antigen	Allergic Subjects			Nonallergic Subjects		
	Number Tested	Number Positive	Percent Positive	Number Tested	Number Positive	Percent Positive
Staphylococcus	200	62	31.0%	100	8	8%
M. catarrhalis	200	48	24.0%	100	6	6%
Pneumococcus	200	23	11.5%	100	5	5%
Streptococcus	200	10	5.0%			
E. coli	200	15	7.5%			
H. influenzae	200	15	7.5%			
Friedlander's bacillus	200	16	8.0%			

TABLE II. BACTERIAL TESTS IN PRIVATE PRACTICE

Dr. Bennett Kraft's Office

Name	Staph. "UBA"	Catarrhalis "UBA"	Pneumococcus "UBA"	Strep. "UBA"	E. Coli "UBA"	Influenzae "UBA"	Friedlander "UBA"
F. G.	0	0	0	0	0	0	0
E. H.	0	+	+	+	+	0	+
L. H.	0	0	0	0	0	0	0
C. H.	0	0	0	0	0	0	0
J. H.	0	0	0	0	0	0	0
G. H.	0	0	0	0	0	0	0
V. H.	+	+	0	0	0	0	0
G. H.	0	0	0	0	0	0	0
E. H.	+	0	0	0	0	0	+
E. I.	+	+	+	0	0	0	0
J.	0	+	0	+	0	0	0
H. J.	0	0	0	0	0	0	0
M. J.	+	+	0	0	0	0	+
C. J.	+	0	+	0	+	0	0
A. J.	+	+	0	0	0	0	0
A. K.	0	0	0	0	0	0	0
M. K.	+	0	0	0	0	0	0
V. K.	0	0	0	0	0	0	0
F. K.	+	0	0	0	+	+	0
F. K.	+	0	0	0	+	+	0
K. K.	0	0	0	0	0	0	0
K. K.	0	0	0	0	0	+	0

RESULTS

Table I records a summary of our observations. Table II is a sample page containing twenty-two of the individual records. To have included all individual records would have required too much space.

Rather early in this study we were impressed by the greater frequency of reactions to the staphylococcus and M. catarrhalis in the patients with an allergic history. Hence, it became desirable to investigate the frequency with which subjects with a nonallergic history would react to these antigens.

It is of interest that Forman[1] and Walker[4] also found that the staphylococcus caused positive skin reactions more frequently than other bacteria which they used.

COMMENT

In presenting this paper we do not mean to imply that immediate positive skin tests such as were obtained in this series are always diagnostic or that they can always be used as a guide to treatment. This is another

problem which is now being investigated. However, these observations do suggest: (1) that immediate reactions to bacterial antigens are not rare; (2) that the staphylococcus and M. catarrhalis cause immediate positive skin reactions more frequently in allergic than in nonallergic patients; (3) that this most controversial question of immediate skin reactions to bacterial antigens should be reopened and studied further; (4) that studies should be carried out with the undenatured antigen with a view to comparing it with other bacterial antigens as a testing agent.

SUMMARY

1. An investigation was made with respect to the frequency of immediate urticarial reactions following intradermal injections of undenatured bacterial antigens.

2. Two hundred patients with histories of allergic symptoms received intradermal injections of seven antigens, and 100 nonallergic patients were tested against staphylococci, M. catarrhalis, and pneumococcus.

3. The staphylococcus caused positive skin reactions in 31 per cent of allergic patients and 8 per cent of nonallergic subjects. M. catarrhalis caused positive reactions in 24 per cent of allergic and 6 per cent of nonallergic persons. The difference in response of allergic and nonallergic subjects to pneumococcus antigen was not proven to be significant when the chi square test was used to measure the significance of the difference.

4. The problem of immediate skin reactions to bacteria should be studied further.

760 Bankers Trust Bldg.

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IMMUNITY TO DIPHTHERIA INDUCED BY A BOOSTER DOSE OF ALCOHOL-REFINED, ALUM-PRECIPITATED TOXOIDS

Based on a Study of Fifty-nine Allergic Children

HOWARD G. RAPAPORT, M.D., F.A.C.A. and M. MURRAY PESHKIN, M.D., F.A.C.A.
New York, New York

DESPITE refinements in technique for injecting detoxified crude bacterial filtrates and alum-precipitated toxoids used in the prophylaxis against diphtheria, frequently disturbing and undesirable systemic reactions occur, especially after a booster dose administered to older children. In a search for a toxoid capable of causing a minimum or no undesirable reactions, we[3] reported, last year, on the use of calcium phosphated and eluted diphtherial toxoids prepared by Parfentjev and his associates.[1] These toxoids were highly purified, contained very little nitrogen, were free from bacillary proteins and were highly antigenic. A booster dose of either of these diphtherial toxoids caused the antitoxin levels to rise as high as 40 units per cubic centimeter of blood.

Despite the elimination of over 90 per cent of the nitrogen in the preparation employed in our previous study, severe local reactions, following a booster dose associated with elevation of temperature, occurred sufficiently often with the calcium phosphated diphtherial toxoid to preclude its use in the immunization of children against diphtheria. However, with the eluted calcium phosphated toxoid, the incidence of reactions following booster doses, especially the febrile reaction in older children, was less than that experienced after the uneluted toxoid, as well as that experienced by another comparable group of children injected with the commonly employed combined diphtherial and tetanal toxoids, alum-precipitated.[2]

The eluted calcium phosphated diphtherial toxoid was regarded as a most satisfactory preparation, and its use pointed to definite progress in lowering the incidence of local, febrile or systemic allergic reactions. However, the search for a toxoid capable of further lowering the incidence and severity of these undesirable reactions led to the use of the alcohol-refined, alum-precipitated toxoids in allergic children. The experiences with this newer toxoid comprise the subject of this communication.

The improved method of refining toxoids for immunizing purposes was developed by Pillemer and his associates.[4] The method consists of the purification and concentration of toxoids by methanol precipitation under controlled conditions of pH, ionic strength and temperature. Both the fluid and the alum-precipitated series of toxoids may be refined by this method.

These toxoids have had their protein nitrogen content greatly reduced so that the nonantigenic nitrogen amounts to less than 0.1 mg. per cent.

From the Children's Allergy Clinic, Mount Sinai Hospital.
Dr. J. M. Ruegsegger of the Lederle Laboratories gave technical assistance in this study.
The preparations of the alcohol-refined, alum-precipitated combined diphtherial and tetanal toxoids and alcohol-refined, alum-precipitated diphtherial toxoid (Purogenated) used in this study were furnished by Lederle Laboratories, Pearl River, N. Y.

These solutions are practically free from bacillary protein. The stability of the solutions has been maintained by the addition of glycine so that these toxoids are not subject to denaturing, an important disadvantage and objection of the previously presented, highly purified toxoids. The alum content of the alum-precipitated series of toxoids has been reduced to 3 to 6 mg. per dose instead of 20 mg. as previously employed.

Pillemer and his associates[4] have demonstrated that in animals these toxoids possess high antigenic potency. Moreover, they have shown that this method of refinement and purification eliminates the allergenic and anaphylactogenic fractions from the toxoids. It is conceivable that these toxoids may reduce very appreciably the reactions noted after human inoculations. This presumption is amply substantiated by the findings noted in this report.

For this communication fifty-nine allergic children with bronchial asthma or hay fever or both were selected for injection with these alcohol-refined, alum-precipitated toxoids. All of these children have been previously immunized with diphtherial toxoid and a number of them with combined diphtherial and tetanal toxoids, alum-precipated. Their average age was thirteen years. The purpose of this investigation was to determine:

1. The incidence of local and systemic reactions in allergic children following a booster dose of highly purified toxoids, in an age group of children in whom unfavorable reactions occur most frequently following a booster dose of crude or ordinary alum-precipitated combined diphtherial and tetanal toxoids or alum-precipitated diphtherial toxoid alone.

2. The time of maximum antitoxin response.

3. The incidence of positive cutaneous tests to the purified toxoids.

MATERIALS AND METHODS

There was a total of 184 samples of blood titrated for diphtherial antitoxin from the fifty-nine allergic children injected witn the booster dose of alcohol-refined, alum-precipitated toxoids. Thirty-four children were injected with combined diphtherial and tetanal toxoids, and twenty-five children with diphtherial toxoid alone. The dose consisted of 0.5 c.c. of either toxoid injected subcutaneously in the upper and outer aspect of the arm.

Neither Schick nor Molony tests were performed before the booster innoculation.

Initially, blood samples were taken from the fifty-nine selected allergic children and their diphtherial antitoxin titers in "American Units" were recorded.

From one week to four months after the booster injection, bleedings on the fifty-nine children were done one or more times and the diphtherial antitoxin values determined. These results are shown in Table I.

TABLE I, DIPHTHERIAL ANTITOXIN TITERS OF FIFTY-NINE ALLERGIC CHILDREN OBTAINED AFTER THE BOOSTER INJECTION OF ALUM-PRECIPITATED, ALCOHOL-REFINED TOXOIDS

Antitoxin Titer, Units per c.c. of Serum Before and After Injection of Toxoid									
Case Number	Before Booster Dose	After Booster Dose of 0.5 c.c.							
		Week	Months						
		1	1		2		3		
1	0.002		0.01		0.1		0.1		
2	0.01	0.2			0.5				
3*	0.01		0.5		(0.5) 1.0				
4	0.01	(0.02) 0.04			1.0		0.5		
5	0.01	0.2	2.0						
6	0.01	(0.2) 0.5	2.0		(2.0) 4.0		(0.2) 0.5		
7	0.02	(0.02) 0.04	0.2		1.0		0.5		
8*	0.02				(0.2) 0.5				
9*	0.02		1.0						
10	0.02	(2.00) 4.0							
11*	0.02		4.0		4.0		2.0		
12*	0.02				2.0		1.0		
13*	0.02						1.0		
14*	0.02				4.0		8.0		
15	(0.02) 0.04	0.5	2.0		(4.0) 8.0		8.0		
16*	0.04	0.2	0.5		1.0				
17*	0.04	(1.0) 2.0							
18*	0.04						4.0		
19*	0.04				0.5		(0.5) 1.0		
20	0.04		(2.0) 4.0		(8.0) 16.0				
21	0.04	4.0	16.0		(16.0) 32.0		64.0		
22	(0.04) 0.1	0.2							
23*	(0.04) 0.1	(0.2) 0.5							
24*	(0.04) 0.1				4.0		1.0†		
25*	(0.04) 0.1	(2.0) 4.0			8.0		16.0		
26	(0.04) 0.1	8.0	8.0		32.0		(8.0) 16.0		
27*	0.1				16.0		8.0†		
28*	0.1		8.0				0.5		
29	0.1				2.0				
30	0.1	(2.0) 4.0	4.0		16.0				
31	0.1	2.0	16.0				16.0		
32*	0.1				8.0		16.0		
33	0.1	8.0	(16.0) 32.0		64.0				
34*	0.2						3.0		
35*	0.2				8.0				
36*	0.2	4.0			16.0		8.0†		
37	0.2	16.0	64.0		16.0				
38*	(0.2) 0.5				8.0				
39	(0.2) 0.5	32.0			128.0				
40*	0.5		(2.0) 4.0						
41*	0.5						8.0†		
42*	0.5				8.0		3.0		
43	0.5	4.0	(4.0) 8.0		32.0		(32.0) 64.0		
44*	0.5		16.0		32.0				
45*	0.5		(32.0) 64.0						
46	0.5		64.0		64.0		64.0		
47	0.5	128.0	128.0						
48*	1.0		16.0		(4.0) 8.0				
49	1.0	8.0			16.0		16.0		
50*	1.0				(128.0) 256.0				
51*	2.0		8.0		4.0				
52*	2.0	32.0							
53	2.0	32.0							
54	2.0	32.0	(32.0) 64.0		128.0		(32.0) 64.0		
55	4.0	16.0							
56*	4.0		16.0				6.0†		
57*	4.0		16.0		8.0				
58*	4.0				(16.0) 32.0		16.0		
59*	8.0				64.0		32.0		

*Asterisk denotes patient was injected with the combined diphtherial and tetanal toxoids. The tetana antitoxin titers in these cases will be reported in a subsequent communication. The case numbers without the asterisk denote that the patients were injected with diphtherial toxoid alone.
†Denotes antitoxin titer recorded four months after the booster injection of toxoid.

TIME OF OCCURRENCE OF MAXIMUM RESPONSE TO THE TOXOID PREPARATION

A review of Table I shows both the alcohol-refined, alum-precipitated combined diphtherial and tetanal toxoids and the alcohol-refined, alum-

precipitated diphtherial toxoid to possess marked antigenic potency. A booster dose of either toxoid causes the diphtherial levels to rise as high as 128 units of antitoxin per cubic centimeter of blood. Moreover, there is no appreciable difference in the diphtherial antitoxin response after a booster injection of either the combined diphtherial and tetanal toxoids and the diphtherial toxoid alone. For this reason there will be no segregation of the maximum diphtherial antitoxin values obtained.

Twenty children were available for diphtherial antitoxin studies one week and from one to three months after the booster injection of toxoid. The maximum antitoxin response occurred after one week in one child, after one month in three children, after two months in twelve children and after three months in four children.

A second group of twenty-one children were available for study one or two months after the booster dose of toxoid, and again two and three months after the booster dose, respectively. The maximum antitoxin response occurred after one month in seven children, after two months in eleven children and after three months in three children.

In a third group of eighteen children only one diphtherial antitoxin titer was done from one week to three months after the booster dose of toxoid. The rise in titer in these children was from four to 128 times above the corresponding antitoxin levels obtained prior to the booster injection.

Thus, of the fifty-nine children in this series, the rise to a maximum diphtherial antitoxin titer was four to 640 times, or an average of 123 times, above the corresponding antitoxin level obtained prior to the booster injection of toxoid. The maximum antitoxin titer ranged from 0.1 unit to 128 units per cubic centimeter of blood and in the majority of patients occurred two months after the booster dose. All children had a rise in diphtherial antitoxin titer after the booster inoculation.

REACTION AND SENSITIVITY

Following the booster injection of the alcohol-refined, alum-precipitated toxoids, 9 per cent of the children experienced slight local reactions, exhibited by erythema, slight local heat and mild tenderness without enlargement of the lymph nodes. All local reactions appeared within twelve to twenty-four hours and reached maximum intensity within forty-eight hours after the injections. As a matter of fact, the local reactions were so mild that the children disregarded them. None showed an elevation of temperature or an allergic reaction. These findings are in marked contrast to the higher incidence and severity of local reactions, to which must be added the systemic reactions, following injections of the commonly employed toxoids[2] and refined eluted calcium phosphated toxoid.[3]

Scratch tests were performed with undiluted fluid alcohol-refined diphtheria and tetanus toxoids. Negative reactions were obtained in all the children.

SUMMARY AND CONCLUSIONS

Fifty-nine allergic children whose average age was thirteen, were primarily immunized against diphtheria in early childhood, and the majority of these children subsequently received one or more doses of the commonly employed diphtherial toxoids. All of these children were given a booster injection of a purified toxoid prepared after the method of Pillemer and his associates. The method of alcohol refinement and purification practically eliminated the allergenic fractions from the toxoids without disturbing its high antigenic potency.

Thirty-four children were injected with the alcohol-refined, alum-precipitated combined diphtherial and tetanal toxoids and twenty-five children with the alcohol-refined, alum-precipitated diphtherial toxoid alone. The dose consisted of 0.5 c.c. of either toxoid.

From one week to four months after the booster injection, bleedings on the fifty-nine children were done one or more times, and the diphtherial antitoxin titer revealed that this new refined toxoid caused a rise in antitoxin as high as 128 units or more per cubic centimeter of blood. The rise in titer occurred in all the children and was from four to 464 times, or an average of 123 times, above the corresponding antitoxin level obtained prior to the booster injection of toxoid. The maximum antitoxin titer ranged from 0.1 unit to 128 units per cubic centimeter of blood and in the majority of patients occurred two months after the booster dose.

Scratch tests with the undiluted fluid alcohol-refined toxoids showed negative reactions in all the children.

Negligible local reactions occurred at the site of the injection in 9 per cent of the children. No child experienced an elevation of temperature or an allergic reaction after the booster injection of alcohol-refined, alum-precipitated toxoid. The alcohol-refined, alum-precipitated diphtherial toxoid, alone or combined with tetanal toxoid, can be currently regarded as the most ideal and reliable preparation for immunization against diphtheria. Moreover, the usefulness of these toxoids are further enhanced since febrile and systemic allergic reactions are practically eliminated following their use.

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7 W. 96th Street
New York 25, N. Y.

AN IMPROVED TISSUE CULTURE TECHNIQUE ADAPTABLE TO CLINICAL TESTING FOR BACTERIAL HYPERSENSITIVITY OF THE TUBERCULIN TYPE

HERMANN BLATT, M.D., FRANK A. NANTZ, M.D., and JEANNE M. REHM
Cincinnati, Ohio

WE have previously described a method of leukocyte culture as a test for bacterial hypersensitivity[6] based upon the fact that the cells from cases of bacterial hypersensitivity are killed *in vitro* by contact with the specific bacterial protein, whereas cells from subjects with anaphylactic, Arthus or pollen-type sensitivity are not killed *in vitro* by contact with the specific protein. To adapt this laboratory procedure to clinical testing a technique is desirable which is as simple as possible, and which eliminates variables other than the leukocyte and the bacterial protein. We have substituted fibrin for plasma and thereby minimized serological factors known to interfere with the test.[1,5,7] The size and shape of the explants of the buffy coat were standardized by using a corneo-scleral trephine. With this technique we have performed several thousand cultures and will report these results in a later paper. The present report concerns an improved and simplified procedure.

Aside from variations in the effect of different sera, which we have largely eliminated, there are other variables. Draper, Ramsey, and Dupertuis[3] reported that there is considerable variation in the areola of buffy coat cultures in different constitutional types. We found several patients in whom we were never able to obtain good areola formation. This made for inconsistent results. Necrotic leukocytes have a stimulating effect on leukocyte migration.[2] To what degree this alters the size and shape of the areola is unknown. Chemotaxis of leukocytes also occasionally causes unequal motion of leukocytes and makes interpretation of the slide culture difficult. Many tissue cells produce a fibrinolysin. We had many tissue cultures in which migration of leukocytes into the fibrin clot may have been prevented or interfered with due to early lysis of the clot. The leukocytes themselves may produce this lytic effect. Favata[4] reports that fibrocytes may be kept viable in a fibrin clot for as long as six weeks without fibrinolysis occurring. Our leukocyte cultures, on the other hand, often result in lysis of the clot within three days. Migration of leukocytes seems to depend upon a fibrinous matrix for support, and an early lysis of the clot may result in a false positive test. Finally, in the separation of the buffy coat a layer of platelets occasionally forms and cannot easily be distinguished from the leukocyte layer. This also may cause false positive readings.

We have therefore modified the procedure of the test in a manner

The bacterial filtrates discussed in this report were supplied through the courtesy of Eli Lilly and Co. Thrombin was supplied by Upjohn Co.
Dr. Blatt and Dr. Nantz are Associate Fellows of the American College of Allergists.

which, we believe, reduces these variables to a minimum. Citrated venous blood is withdrawn and the buffy coat separated as previously described.[6] The entire buffy coat is placed in 1 c.c. of Ringer's solution, and is then vigorously shaken for about one minute. The suspension is allowed to stand at room temperature or in the incubator for one hour. It is again shaken and allowed to stand for five minutes. With a capillary pipette the supernatant layer of suspended cells is withdrawn and one drop each of the cell suspension, the bacterial filtrate in proper dilution, and one-tenth full strength thrombin are mixed together on an ordinary glass slide ringed with Vaseline. The mixture is covered with a cover slip and the culture incubated overnight or for eighteen hours. If the test is positive, the cells are necrotic. If negative, the cells remain viable.

580 Doctors Bldg.

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COMMENT

In an article entitled "Sensitization to Petrolatum in Ointment Bases," published in the September-October, 1948 issue, of ANNALS OF ALLERGY, the authors, Dr. Samuel J. Levin and Dr. Selma S. Moss, reviewed six cases and cited four additional ones of patients sensitive to petrolatum. The presentation does a great service in that it calls attention to one of the pitfalls in managing patients who have an "eczema" or "dermatitis" of any etiological background.

I cannot agree, however, with the implication of sensitization or allergic reaction to petrolatum or related substances. The "usage test" (rubbing in of agent at intervals) which the authors employ, is carried out on areas involved in the disease process. I infer that the tests were negative when done on uninvolved skin areas. In the authors' words they "may be positive on affected sites and later negative on the same healed sites."

In experiments recently reported by me,[1,2] the role of a second contactant upon sites of healed induced specific dermatitis was studied. In forty-two subjects the healed areas of contact dermatitis were tested with a second unrelated contactant, which was known to be a good sensitizer, and thirteen typical positive reactions were obtained. Control tests were negative on adjacent uninvolved skin. The response to the second contactant could not be considered as a specific or allergic one, but rather as a non-specific effect. It was concluded that a healed site of specific dermatitis was more reactive or responsive to a secondary chemical stimulus than was uninvolved skin.

I feel that the role of petrolatum in the cases under discussion was that of a non-specific agent, and that the term "sensitization to petrolatum" should not be employed. This criticism on terminology does not, however, detract from the value of the article.

MAX GROLNICK, M.D., F.A.C.A.
555 Ocean Avenue
Brooklyn, N. Y.

[1]An Evaluation of the Patch-Test Based on Experimental Findings. Read before the meeting of the American College of Allergists, New York, 1948.
[2]Studies in Contact Dermatitis, VII. The Response of Healed Specific Dermatitis Sites to Stimulation with Another Contactant. *Journal of Allergy*, 19:298, 1948.

THE ORIGIN OF PATTERNS OF ALLERGIC SENSITIZATION

ROGER P. WODEHOUSE, PH.D.
Pearl River, New York

ALLERGIC sensitizations are rarely, if ever, single. Among hay-fever sufferers, for example, sensitization to the pollen of one species of plant invariably implies sensitization to that of some or many of its phylogenetically related species, apparently depending, at least in part, upon the degree of the patient's sensitivity. Besides these, however, there are nearly always sensitizations to totally unrelated substances, frequently including pollens of all biological groups of hay-fever plants, and even animal danders, and foods of both vegetable and animal origin. Multiple sensitizations thus fall into two fairly distinct categories, those to related substances and those to unrelated substances.

Apparently the cross reactions that are obtained within restricted biological groups are due to chemical similarities among related species. They vary widely with different patients but tend to follow a pattern. Some patients are highly discriminating, reacting only to species of a narrowly restricted biological group, others to those more distantly related, frequently including substances to which they had never previously been exposed. Nevertheless these sensitization patterns, whether restricted or broad, tend to correspond to those of the biological classification as if the sensitizations were interdependent. On the other hand, sensitizations to unrelated substances appear to be random and inconsistent among different patients, as if independently acquired. Thus, a patient who is sensitive to short ragweed is invariably sensitive to tall and western ragweeds. He is generally sensitive to all the other members of the ragweed group and frequently to other members of the composite family. On the other hand, he may or may not also be sensitive to timothy, plantain or some of the animal danders.

It has been shown (Wodehouse, 1948), through cross neutralization of passive transfer sites, that the patterns of hay-fever sensitization are characterized by a dominating or strong sensitization accompanied by a variable number of subordinate or weaker sensitizations. In passive transfer all can be neutralized by the allergen of the dominant sensitization, but the latter can only be neutralized by its homologous allergen or those of very closely related species, presumably carrying identical antigens. None of the unrelated subordinate allergens can neutralize the dominant sensitization. But all of them can neutralize sensitizations against each other, at least partly, either unilaterally or reciprocally and without regard to biological relationships.

Similar observations have been recorded by other investigators, but as far as I am aware no satisfactory explanation has been offered for their occurrence. Hooker (1944) reports the case of a woman who suffered

From the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y. Dr. Wodehouse is an Associate Fellow of the American College of Allergists.

asthma from the slightest contact with any spitz dog, but never from her own cocker spaniel which had lived with her for seven years. This patient also had hay fever and was known to be skin sensitive to ragweed pollen, dog dander, feathers and house dust; eating grapefruit brought on severe asthma. Her symptoms were ameliorated by dust precautions, abstinence from citrus fruits and treatment with ragweed extract. Considered in the light of our patterns of sensitization, it seems probable that this patient's dominant sensitization was either to dog dander or to ragweed, most probably the former through earlier contact with a spitz, and that the ragweed and other sensitizations were subordinate and developed later. The author points out that the domestic dog is polyphyletic, having arisen through hybridization from a number of species, not all of which are known, and he produces convincing evidence that the specific antigens are inherited as unit characters.

Hooker tested the serum of another dog-sensitive patient by passive transfer and cross neutralization. It was found that boxer dander neutralized the sites to test with "stock dog" and poodle danders. The stock dander neutralized only to itself; poodle neutralized completely only to itself, but partly to all the others. But scottie neutralized completely to all. This is good evidence that some of the different breeds of dog may be antigenically as different as species ordinarily are, and that with this serum the strongest or dominant sensitization was to scottie dander.

Of similar interest in this connection is the report of Simon (1942). He found that the reagins of four patients who were sensitive to sera of such diverse mammals as horse, cow, dog, guinea pig, hog, rat, rabbit, sheep, cat and porpoise, could in each case all be neutralized by one mammalian serum, those of two of the patients by that of dog, of one by that of horse, and of one by that of sheep. Elsewhere the author (1942) notes that antibodies for a given mammalian serum obtained from one patient, were neutralized by several other mammalian sera, whereas antibodies for the same serum, obtained from another patient, were not entirely neutralized by the same sera. "This fact," he says, "definitely proves that the antibodies for this particular mammalian serum obtained from two different sources are not identical. These differences in antibodies may be partly explained by assuming that the antibodies were brought into existence as the result of stimulation by different allergens."

Simon (1946) reported that of ten cases sensitive to animal danders, sera and muscle, with six, all transfer sensitizations were neutralized by dog dander; with two, dog serum and dog muscle were also able to neutralize all sensitizations; in two cases no single allergen was found which could neutralize all sensitizations. With the first six the dominant sensitization was obviously to dog dander. With the next two it was also to dog dander but less highly specific, so that the serum and muscle of the same animal were also included. In the latter two the allergen of the dominant sensitization did not happen to be among those tested. The author, in com-

menting on these observations, says, "A substance which neutralizes all the antibodies in a patient's serum is thereby proved to be *capable of being* the only sensitizing allergen, i.e., the only substance which, when the patient is exposed to it, stimulates the production of hypersensitiveness to itself and to related allergens. A substance which does not neutralize all the antibodies in a patient's serum is thereby proved to be incapable of having produced the hypersensitiveness." In other words, in cases of multiple sensitization the antigen of the dominant sensitization could be the only sensitizing substance. This seems to me not quite to harmonize with the author's earlier statement that the antibodies were brought into existence as the result of stimulation by different allergens, unless one hypothecates a double origin of the sensitizing antibody.

Commenting on these observations of Simon, Landsteiner (1945) says, "The skin reactions observed in allergic human beings, extending somewhat unexpectedly to all mammalian sera tested, can be due to antibodies of wide reaction range whose formation is perhaps favored by long continued sensitization; multiple sensitization may be a contributing factor."

All of these observations strongly suggest that the patterns of hay-fever sensitization may reflect the antigenic structure of a major allergen.

On the other hand, there is convincing evidence that the control of the patterns of allergic sensitization resides in the antibody. Clarke (1927) "showed that a strong reaction of one antigen in a passive transfer site might render the site inactive on subsequent tests with other antigens. His experiments suggest that cross neutralizations depended on the relative concentrations of antibodies."* At a later date Clarke (1937) said that when the reagin was present in a weak concentration it was subject to neutralization by almost anything, whereas where the reagins were present in sufficient concentration so that two or more skin tests were necessary to neutralize, no matter what was done, the stronger reaction persisted. Harkavy and Witebsky (1935), in their study on the absorption of reagins in the serum of a patient sensitive to corn, timothy and tobacco, found that passive sites neutralized by timothy or tobacco were neutralized to corn but not to each other. Nor would corn neutralize the sites against tobacco and timothy. The authors say, "It may therefore be concluded that . . . the major reagins were those for tobacco and timothy. These were specific and independent." I have not yet encountered a serum with more than one major or dominant sensitization, and doubt its occurrence. Certainly in this case tobacco and timothy both dominate corn, but the fact that neither one can neutralize the reagin of the other suggests, in the light of these studies, that both are subordinate to some other sensitization not discovered by the authors.

Sherman and Stull (1938) from a series of carefully controlled studies concluded that, "it is apparent that the cross neutralization reactions obtained depended upon the serum tested and did not represent a constant

*This statement, made by Clarke before the American Association of Immunologists, appears not to have been published until 1938 by Sherman and Stull, from whom it is here quoted.

relationship between the antigens," and that "Antigens which react strongly with a serum tend to neutralize the reactions to antigens reacting less actively."

It seemed to the present author, as already expressed (1948), reasonable to suppose that cross neutralizations and the ability of the predominant allergen to neutralize all the sensitizations of a serum took place because the allergen responsible for the dominant sensitization carried, besides its main specific antigen, a number of minor antigens common to other species, as shown by precipitin absorption to be the case with egg albumen, for example (Hooker and Boyd 1934, Landsteiner and Van der Scheer, 1945). If this were true of allergic sensitization the predominant allergen must carry antigens or antigenic determinants for all of the patient's sensitizations, and its antigenic complex would set the pattern of sensitization. All those patients having the same dominant sensitization would of necessity have somewhat similar subordinate sensitizations since they would be drawn from the same source. In order to put this to the test, the sera of three hay-fever cases, in which the dominant sensitization is to Russian thistle, have been examined and compared for resemblances, and these in turn compared with a fourth serum, of which rabbit dander is the dominant sensitizing agent.

The methods followed in the present investigation were essentially the same as already reported (1948). For the most part the *in vivo* desensitization method was employed, and the reciprocal tests done on the same recipient at the same time. This was to facilitate comparison of the reactions to the material when used in first tests with those of the same material when used in the reciprocal tests. Injections were all made and the reactions read by the same person, kept in ignorance of the materials being used. They were recorded at time of reading as the average diameters of the wheals and over-all diameters of the erythemas. If the second extract produced a reaction essentially the same as the same material did in a fresh site, the sensitization of the retested site was regarded as unimpaired by its reaction to the first material, and was recorded in the tables as +. If the second extract produced only a doubtful or borderline reaction, or none at all, the site was regarded as neutralized by the first reaction, and the absence of reaction to the second material was recorded in the table as O. Reactions between these limits were regarded as indicating partial neutralization. These were generally repeated on another recipient, and unless they reappeared definitely + or O, they were recorded as ±.

For the preparation of the sera, blood was taken with a 50 c.c. syringe, allowed to clot at room temperature, stored overnight at 7° C. The clot was then loosened from the walls of the containers and the serum separated by centrifuging. It was then sterilized by Seitz filtration and sterility demonstrated according to the methods of the National Institute of Health.

Immediately after filtration the serum was frozen in ½ c.c. amounts and stored at a temperature of about -65° C. All sera used in these experiments were collected in 1944, except Spri in 1947. Preserved in this fashion none has shown any loss of activity.

If sera are to be stored for any length of time, it is more economical to dry them, and quite as satisfactory. Other sera than those used in these experiments were collected at the same time and lyophilized and kept without noticeable deterioration to the present time (four years). Also a ragweed sensitive serum collected and dried *in vacuo* by Dr. Coca in June, 1931, when tested in March, 1945, a comparison of the

TABLE I

Sites desensitized with:	Typical reactions: Wheal	Typical reactions: Erythema	Retest Reactions: CHENOPODIACEAE	Russian thistle	Summer cypress	Lambsquarters	Ann. saltbush	Shadscale	AMARANTHACEAE	Carelessweed	Western waterhemp	Spiny amaranth	GRAMINEAE	Bermuda grass	Timothy	COMPOSITAE	Western ragweed	Bur ragweed	Sagebrush	MISCELLANEOUS	Mesquite	Black walnut	Sheep sorrel
CHENOPODIACEAE																							
Russian thistle	9	30			0	0	0	0		0		0		0	0		0	0		0			
Summer cypress	9	35		0		0	0	0		0		0					0	0		0			
Lambsquarters	7	35		0	0					0													
Ann. saltbush	11	60		0	0					0													
Shadscale	8	35		±	+					±													
AMARANTHACEAE																							
Carelessweed	11	50		0	0	0	0	0			0	0					0	0		0			
Western waterhemp	9	15								±													
Spiny amaranth	8	30		±						±													
GRAMINEAE																							
Bermuda grass	10	40		+											0			0					
Timothy	8	18		+										±									
COMPOSITAE																							
Western ragweed	8	40		+	+					+													
Bur ragweed	8	50		±	0					+													
Sagebrush		0																					
MISCELLANEOUS																							
Mesquite	5	30		+	+					+													
Black walnut		0																					
Sheep sorrel		0																					

Table I, Bol serum. In this and the two following tables, in which Russian thistle is the dominant sensitization, the pollen species are arranged in the same sequence to facilitate comparison. Hence in each table some species appear which failed to give reactions with the serum or which were not used in the experiment. The sequence is to some extent phylogenetic as indicated by the headings in the table.

The table tells, reading the first line, for example, that sites sensitized with this serum when neutralized by Russian thistle fail to react to any of the pollens with which they were tested; or, reading the vertical column under Russian thistle, it tells that summer cypress, lambsquarters, annual saltbush and carelessweed neutralize the sites to test with Russian thistle, hence are reciprocal with it, but nothing else can completely neutralize the sites to it.

The table is a compilation of about twelve protocols comprising about seventy neutralization experiments.

reactions obtained with his diagrams of those obtained fourteen years earlier showed no loss of sensitizing power.

The results of cross neutralization experiments with four sera are summarized in Tables I through IV.

Bol Serum.—The donor of this serum was a resident of Highland, California, where he suffered severely from seasonal hay fever. In direct intracutaneous test he reacted to pollens of some of the grasses—strongest to Bermuda—to amaranth-chenopods, ragweeds, mugworts, walnut, mesquite, oak, horse, dog and rabbit danders, but not to any foods. When his blood was taken he was being treated with extracts of twelve different pollens, representing all the different groups, but two-thirds of them were of the amaranth-chenopod group, because it was known that his symptoms were due principally to the pollens of these plants.

His serum transferred sensitivity to thirteen different pollens (Table I) but not to

TABLE II

Sites desensitized with:	Typical reactions: Wheal	Typical reactions: Erythema	Retest Reactions: CHENOPODIACEAE	Russian thistle	Summer cypress	Lambsquarters	Ann. saltbush	Shadscale	AMARANTHACEAE	Carlessweed	Western waterhemp	Spiny amaranth	GRAMINEAE	Bermuda grass	Timothy	COMPOSITAE	Western ragweed	Bur ragweed	Sagebrush	MISCELLANEOUS	Mesquite	Black walnut	Sheep sorrel
CHENOPODIACEAE																							
Russian thistle	10	45			0	0	0			0									0		0		
Summer cypress	10	40		0			0			0									0				
Lambsquarters	6	35		+			0												+				
Ann. saltbush	9	45		0	0	0				0													
Shadscale		0																					
AMARANTHACEAE																							
Carlessweed	9	35		±	0		0												±				
Western waterhemp		0																					
Spiny amaranth		0																					
GRAMINEAE																							
Bermuda grass		0																					
Timothy		0																					
COMPOSITAE																							
Western ragweed	6	10																					
Bur Ragweed		0																					
Sagebrush	16	30		+	±	±	±			±													
MISCELLANEOUS																							
Mesquite	8	25		+																			
Black walnut																							
Sheep sorrel		0																					

Table II, White serum. For explanation see Table I. With this serum sagebrush approaches the status of a submajor. The meagre reactions of this serum did not permit the sagebrush tests to be carried out further. They should be compared with Bermuda grass in Ra serum and ragweed in Phil serum.

The table is a compilation of about ten protocols or about forty neutralization experiments.

that of sagebrush, walnut, sorrel nor any animal danders to which he had been found sensitive by direct test. Cross neutralization tests showed that Russian thistle neutralized all sensitivities, but sensitivity to it could not be completely neutralized by any pollen outside of the Russian thistle group. Within the group, however, it was neutralized by summer cypress, lambsquarters, annual saltbush and carelessweed. These four pollens are thus reciprocally neutralizing with Russian thistle and with each other as far as tested. Moreover they behave in almost every respect as if they were antigenically identical.

Bermuda grass and timothy failed to react at the concentrations used for all the other tests, viz., with the serum 1:25 and extract 1000 units per c.c., but when the serum was used undiluted and the extracts at 2000 units, reactions were obtained.

White Serum.—The donor of this serum was a resident of Lethbridge, Alberta, where she had severe hay fever of the late summer type. By direct scratch test she reacted to Russian thistle 3+, sagebrush 4+, summer cypress 3+, pigweed 2+, lambsquarters +, ragweed ±.

Russian thistle was found to neutralize all passive sensitizations (Table II), and nothing outside of its group could neutralize the Russian thistle sensitization. Within the group summer cypress and annual saltbush as with Bol serum, were reciprocally neutralizing with it and with each other, and behaved alike in other respects, but

TABLE III

Sites desensitized with:	Typical reactions: Wheal	Typical reactions: Erythema	Retest Reactions: CHENOPODIACEAE	Russian thistle	Summer cypress	Lambsquarters	Ann. saltbush	Shadscale	AMARANTHACEAE	Carlessweed	Western waterhemp	Spiny amaranth	GRAMINEAE	Bermuda grass	Timothy	COMPOSITAE	Western ragweed	Bur ragweed	Sagebrush	MISCELLANEOUS	Mesquite	Black walnut	Sheep sorrel
CHENOPODIACEAE																							
Russian thistle	9	50			0		0	0		0	0			0	0			0	0		0		0
Summer cypress	7	35		+							0												
Lambsquarters	8	30		++																			
Ann. saltbush	9	35		0										+	0								
Shadscale	6	20		+	+																		
AMARANTHACEAE																							
Carelessweed	4	10		+							0			+	0								
Western waterhemp	6	35		+	0					±				+	0								
Spiny amaranth																							
GRAMINEAE																							
Bermuda grass	9	55		+	0		0			0	0				0				0			0	
Timothy	7	40		+			+			0	0			+					0			0	
COMPOSITAE																							
Western ragweed	6	18			+																		
Bur ragweed	7	25		+																			
Sagebrush	9	35		+										+	0								
MISCELLANEOUS																							
Mesquite	10	50		+																			
Black walnut	7	30												+	±								
Sheep sorrel	9	40		+																			

Table III, Ra serum. For explanation see Table I. In this serum Russian thistle is reciprocally neutralizing only with annual saltbush. Bermuda grass is subdominant, encroaching upon the dominant group to the extent of completely dominating annual saltbush, a reciprocal of Russian thistle. Compare with bur ragweed in Phil serum. The table is a compilation of about thirteen protocols or about seventy-five neutralization tests.

here the resemblances between the two sera end. Lambsquarters and carelessweed are not reciprocal with Russian thistle, as in Bol serum. And shadscale, which was reciprocal with Russian thistle in Bol serum, does not even give reactions here. Bermuda grass and timothy failed also, even at increased concentration. Nor did the ragweeds give appreciable reactions. On the other hand, sagebrush gave consistently larger reactions than Russian thistle. Nevertheless it failed to neutralize the Russian thistle sensitization.

Ra serum.—This has been reported on before. However, it has been further studied since. For this reason, and to have it at hand for comparison with the others, it is shown again here (Table III). The donor was a resident of Los Angeles, suffering from hay fever during most of the summer.

By direct intracutaneous test he reacted to almost every pollen tried, including sixteen species of grass, the ragweeds, amaranths and chenopods. It was concluded from his history and tests that his hay fever was primarily due to the pollen of grasses. When his blood was taken he was being treated with extracts of seven species of grass and a heterogeneous mixture of other things in an attempt to cover all his sensitizations.

As with the other sera, Russian thistle neutralized the passive sites against all

allergens, while sensitization to it could not be neutralized by anything outside of its group.

Within its group Russian thistle has only one reciprocal, annual saltbush. It is here not even reciprocally neutralizing with summer cypress with which it was reciprocal in both the other sera.

This serum reacts to more pollens outside of the Russian thistle group than did the other two, including sheep sorrel, the ragweeds and black walnut, which failed to give reactions in one or both the other sera. However, its most outstanding characteristic lies in its sensitizations to Bermuda grass and timothy. Bermuda grass is conspicuously predominant over timothy. In fact it dominates everything but Russian thistle, and would be mistaken for the dominant sensitization of the serum were it not known that its sensitization is abolished by Russian thistle but not the reverse. The relationships between timothy and Bermuda grass here are essentially what they were in Rod serum (1948), where Bermuda was the sole dominant and timothy was an undistinguished subordinate, entirely different from the situation in Bol serum (1948), of which timothy was the dominant sensitization. In other words, Bermuda grass, though subordinate to Russian thistle, behaves like a dominant in all other respects. Since this is a fairly frequent occurrence, I suggest that such be called a subdominant sensitization. This condition accords with the fact that the patient's clinical symptoms were mainly due to the pollens of the western grasses among which Bermuda is the most conspicuous.

When we compare the reactions and cross neutralizations of these three sera, we seek in vain for resemblances among their patterns which could indicate that they are controlled by the antigenic structure of the dominating allergen. Even the relations of Russian thistle with members of its own chenopod-amaranth group are different in all three sera. With Bol serum Russian thistle has three reciprocals, with White two, with Ra one. Outside of this group the differences are still greater. Thus the possibility of the sensitizations of all three of these sera being controlled by the antigenic structure of Russian thistle is extremely remote.

On the other hand, the patterns of sensitization of these three sera bear definite relations to the environmental contacts of their donors. It is known that Ra owed his symptoms primarily to grass pollen, and he lived in a region where Bermuda grass is the prevalent pollen. His cross reactions show that Bermuda grass acts as a subdominant, second only to Russian thistle, even taking precedence over other members of the Russian thistle group. On the other hand, White lived in a region where Bermuda grass does not grow, but where sagebrush is one of the principal causes of hay fever. Correlated with this, her serum shows no trace of sensitization to Bermuda grass but a marked, almost subdominant sensitization to sagebrush. Bol's clinical symptoms were easily recognized as being due to the pollens of the Russian thistle group. Correlated with this, his strongest sensitizations are confined to this group. Outside of the group his strongest sensitization is to Bermuda grass, a plant with which he is in contact throughout the summer. These observations seem to be impelling evidence that the patterns of sensitization are largely, if not entirely, controlled by environmental contacts.

It is difficult to imagine the pollen of Russian thistle carrying a large

TABLE IV

Sites desensitized with:	Typical reactions: Wheal	Typical reactions: Erythema	Retest Reactions: EPIDERMALS: Rabbit dander	Guineapig dander	Horse dander	Feathers	COMPOSITAE: Short ragweed	Western ragweed	Bur ragweed	Slender ragweed	Sagebrush	Cocklebur	Burweed	Marshelder
EPIDERMALS														
Rabbit dander	16	40		0	0	0	0	0	0	0	0			
Guineapig dander	8	40	+		0	0	+	±	+	0	0			
Horse dander	7	45	+	+		0	+	+	+	+	+			
Feathers	7	40	+	±	0		+		+		±			
COMPOSITAE														
Short ragweed	10	60	+	±	0	0		0	0	0	0	0	0	0
Western ragweed	10	45	+	±	0		0		0		0			
Bur ragweed	15	65	+	0	0	0	0	0		0	0			
Slender ragweed	8	37	+	+	0		0		0		0			
Sagebrush	10	40	+	±	0	0	+	+	0	0		0	0	0
Cocklebur	7	40					±				0			
Burweed	7	40					+				0			
Marshelder	6	30					±				0			

Table IV, Phil serum. For explanation see Table I. The dominant sensitization of this serum is rabbit dander. Ragweed is subdominant. Only substances related to the dominant and subdominant allergens give reactions. Rabbit dander has no reciprocals, whereas all the ragweeds are reciprocal with each other, not however, with sagebrush, cocklebur, burweed and marshelder. The ragweeds encroach upon the animal danders. Bur ragweed dominates everything except rabbit dander.

The table is a compilation of about sixteen protocols comprising about seventy-five tests.

enough assortment of determinants to satisfy the specific requirements of all possible environments. It is still more difficult to imagine an animal dander being similarly provided with antigenic determinants for a variety of danders and pollens, as in the following serum.

Phil Serum.—The donor of this was a physician of Los Angeles, where he suffered severely from hay fever throughout most of the summer. By direct intracutaneous test he was found to be sensitive to all the pollens with which he was tested, including the grasses, composites, members of the chenopod-amaranth group, California black walnut, poplar and oak. He also reacted to wheat, eggs, orris root and common animal danders, particularly rabbit, to which a 4+ scratch reaction was recorded. When his blood was taken he was being treated with a combination extract of fourteen different pollens, representing all groups. The animal danders and other non-pollen allergens were not included since it was obvious that they played no part in the etiology of his hay fever, which showed itself, by its seasonal occurrence, to be primarily due to pollens.

When this serum was used in passive transfer at a dilution of 1:10 and tested with allergens of 1000 units c.c., only nine sensitizations could be demonstrated (Table IV). It proved negative to all the grasses, amaranths, chenopods and trees, also to cotton seed, dog and cat danders, wheat, wool and orris root, to all of which the patient had reacted by direct test.

Rabbit dander neutralized all sensitizations in the passive sites, and nothing had any effect on the rabbit sensitization. It is the sole dominant with no reciprocals, not even among the other epidermal allergens.

TABLE V

Sera	Allergens	1st Test *1000 u.p.c. w	1st Test *1000 u.p.c. e	2nd Test 2000 u.p.c. w	2nd Test 2000 u.p.c. e	Reciprocal tests Allergens	Reciprocal tests 1000 u.p.c. w	Reciprocal tests 1000 u.p.c. e
Phil 1:5 + Normal	Rabbit dander†	15	50	0		Short ragweed	5	0
Spri 1:5 + Normal	Rabbit dander	5	0	0		Short ragweed	11	45
Spri 1:5 + Phil 1:5	Rabbit dander	15	45	0		Short ragweed	5	0
Spri 1:5 + Phil 1:5	Short ragweed	12	40	0		Rabbit dander	9	40
Phil 1:5 + Normal	Short ragweed	10	35	0		Rabbit dander	9	40
White 1:2 + Normal	Russian thistle	9	35	0		Sagebrush	5	0
Par 1:8 + Normal	Russian thistle	7	20	0		Sagebrush	10	40
Par 1:8 + White 1:2	Russian thistle	10	35	0		Sagebrush	5	0
Par 1:8 + White 1:2	Sagebrush	11	30	0		Russian thistle	10	15
White 1:2 + Normal	Sagebrush	9	30	0		Russian thistle	9	25
Bol 1:2 + Normal	Russian thistle	11	45	5	0	Bermuda grass	5	0
Rod 1:5 + Normal	Russian thistle	12	40	7	12	Bermuda grass	12	40
Bol 1:2 + Rod 1:5	Russian thistle	7	30	6	8	Bermuda grass	14	50
Bol 1:2 + Rod 1:5	Bermuda grass	11	25	7	10	Russian thistle	10	12
Rod 1:5 + Normal	Bermuda grass	11	30	6	0	Russian thistle	7	0
Phil 1:20 + Normal	Rabbit dander	10	60	0		Short ragweed	6	10
Spri 1:4 + Normal	Rabbit dander	5	7	0		Short ragweed	8	60
Spri 1:4 + Phil 1:20	Rabbit dander	10	60	0		Short ragweed	10	45
Spri 1:4 + Phil 1:20	Short ragweed	10	50	0		Rabbit dander	7	12
Phil 1:20 + Normal	Short ragweed	8	45	0		Rabbit dander	10	50

*One unit = 0.00001 Mg. N.
†Rabbit dander used at a concentration of 100 units per c.c.

Table V. Cross reactions with combined sera. Phil and Spri sera were used at a dilution of 1:5, White 1:2 and Par 1:8. These were combined in pairs in equal parts. As controls the individual sera were combined with normal serum, which had been proved to be nonreactive with the allergens used. The combinations were used to sensitize sites by injecting 0.05 c.c. intracutaneously. The sites were tested at intervals of twenty-four hours by injecting 0.01 c.c. of the allergens indicated. The reactions were read after twenty minutes and recorded as the diameters of the wheals (w) and of the erythemas (e). Wheals with inconspicuous erythemas or none at all, though recorded as read, are interpreted as negative.

Each combination of sera is given two widely different dominant sensitizations. Reciprocal cross neutralization tests show that in each combination only one prevails.

Though the ragweeds are subordinate to rabbit dander in this serum they are all reciprocally neutralizing, and short and western ragweed are predominant over the ragweed relatives and sagebrush, which is just the way they behave when in the major position, as in Spri serum (1948). Short, western and bur ragweed also predominate over guinea pig, horse dander and feathers, showing that these three epidermal allergens are antigenically distinct from rabbit dander, which is in harmony with their lack of reciprocity with rabbit dander in the predominant position.

Since ragweed, regarded in the light of antigenic determinants, behaves here like a major allergen in all its contacts, except those with rabbit dander, it would have to be acting through its major antigen. And if these sensitizations were all determined by the antigenic complex of the dominant allergen, rabbit dander would have to bear the major antigen of ragweed which it obviously does not or it would react with all ragweed cases. Hence rabbit dander is *incapable of being* the only sensitizing agent of this serum.

At this stage in the investigation, it seemed desirable to put this idea to experimental test. Accordingly, combinations were made of sera with

widely different dominant sensitizations. For the first were used Phil and Spri, combining rabbit and ragweed dominant sensitizations; for the second, White and Par, combining those of Russian thistle and sagebrush; for the third, Bol and Rod, combining those of Russian thistle and Bermuda grass. Each combination serum is thus given two dominant sensitizations. These combinations were then used to sensitize sites, and reciprocal neutralizations done with the antigens of their given dominant sensitizations (Table V). In no case did the combination serum maintain two dominant sensitizations. In the Phil-Spri combination, rabbit dander assumed dominance over ragweed; in the White-Par combination, Russian thistle assumed dominance over sagebrush; and in Bol-Rod combination, Bermuda grass assumed dominance over Russian thistle. And we have the curious phenomenon of rabbit dander appearing to neutralize the ragweed sensitization which is dominant in the Spri serum, and this in spite of the fact that it does not even cause a reaction with this serum when alone.

The explanation of this was not far to seek. The Phil-Spri combination was tried over again, but with the relative concentrations of the sera altered. Phil serum, which had contributed the dominant rabbit sensitization, was diluted to 1:20, and Spri serum, which had contributed the subordinated ragweed sensitization, was increased in concentration to 1:4, and the two sera combined in equal amounts. Thus favored, the ragweed sensitization assumed just as complete dominance over the rabbit as the rabbit had over the ragweed when the two sera were used in equal strengths (Table V, lower fourth). Obviously it is not reagin neutralization that we are dealing with here but tissue exhaustion. A reaction through the stronger reagin exhausts the site of its ability to react through any weaker reagin. In the White-Par combination, the Russian thistle reagin is stronger than the sagebrush reagin; and in the Bol-Rod combination the Bermuda reagin is stronger than the Russian thistle reagin.

On the other hand, if regarded in the light of antigenic determinants, we may assume that Russian thistle has antigenic factors, *A* and *B*, which react with antibodies, *a* and *b* in White serum, leaving the site completely neutralized, and that sagebrush has factors, *C* and *B* of which *B* can react only with the *b* factor in the serum, leaving *a* still free to react with *A* of Russian thistle. This satisfies the condition of dominance in which Russian thistle neutralizes the sites to test with sagebrush, but sagebrush leaves them active to Russian thistle.

Russian thistle	White Serum	Sagebrush
A	*a*	*C*
B	*b*	*B*

With Par serum this condition is reversed. Thus, Par has antibodies *c* and *b* corresponding to *C* and *B* antigenic determinants of sagebrush.

Russian thistle	Par Serum	Sagebrush
A	*c*	*C*
B	*b*	*B*

When sagebrush is applied to the site, *C* and *B* neutralize *c* and *b* anti-

bodies, leaving the site completely inactivated. But when Russian thistle is applied, only the *b* is used up leaving *c* free to react with the *C* of sagebrush.

Combining the sera, White-Par, gives the combination an antibody complement of *a, bb, c.*

Russian thistle	White + Par	Sagebrush
A	*a*	*B*
B	*bb*	*C*
	c	

Sagebrush reacting with it, leaves *a* free to react with Russian thistle, which suits the facts. But Russian thistle reacting with it leaves *c* free to react with sagebrush, which does not suit the facts because the experiment shows that Russian thistle neutralizes the site to sagebrush.

If we reverse the procedure and ascribe to White serum antibodies *a, b, c,* to Par *a* and *b,* and to Russian thistle antigenic determinants, *A, B, C,* and to sagebrush *A* and *B,* which satisfies the requirements of the reactions of the combined serum, a similar process of reasoning would require that Par serum when alone be neutralized by either sagebrush or Russian thistle, which is false because we have seen that Russian thistle does not neutralize a Par site to test with sagebrush.

I invite the reader to postulate any assortment he cares to of antibodies and antigenic determinants that will satisfy any of the reactions shown in Table V. I have found it an absorbing exercise, but it comes out that it the postulates satisfy the reactions taking place with the sera separately, they invariably lead to fallacy when applied to the reactions obtained in combination, and vice versa.

It thus becomes no longer necessary to postulate multiple determinants or to hunt for heterogenetic antigens in an effort to explain the complicated results of cross neutralizations. Each sensitization is separately acquired, but when they exist together, whether naturally or artificially combined, it is the nature of the neutralization or desensitization reaction that the antigen of the stronger sensitization takes precedence over those of all weaker than it. According to which allergen neutralizes which reagin, the sensitizations can be arranged in a scale of dominance. Presumably, among the subordinate antigens and reagins those which are reciprocally neutralizing, as summer cypress and bur ragweed in Bol serum, or timothy and carelessweed in Ra serum, are approximately equal in the scale of dominance, but why others should be only partially mutually neutralizing, as ragweeds with guinea pig dander in Phil serum, and sagebrush and carelessweed in White serum, still remains unexplained.

The method of cross neutralization in passive transfer sites cannot be used as a means of antigenic analysis, and is useless in discovering biological relationships, except through reciprocal relations with the major sensitization. On the other hand, it furnishes a means of determining the relative strengths of the reagins in a given serum. Moreover, by combing

two sera possessing different dominant sensitizations, the strengths of dominant reagins of different sera may be compared. And this appears to offer a method of standardizing one serum against another, even with reagins to unrelated allergens, and consequently of standardizing one antigen against another, even though unrelated.

SUMMARY

The patterns of allergic sensitization in sera having the same dominant sensitization show no tendency to be stereotyped, as if governed by the antigenic complex of the dominant allergen. Instead they reflect the character of the patient's environment as if all sensitizations were acquired independently of the dominant sensitization, through antigenic contacts with his environment. The subordinate sensitizations and allergens may be mutually or unilaterally neutralizing and may be arranged in a descending scale below the dominant sensitization according to which allergen neutralizes which sensitization.

When two sera possessing different dominant sensitizations are combined and used in cross neutralization tests, one of the dominants is most likely to assume a subordinate position, so that the combination serum has only one functional dominant sensitization. That the stronger reagin of the two in such combination sera assumes the dominant position is shown by the fact that their position can be reversed by appropriately reducing the amount of the serum contributing the sensitization which assumed dominance.

The method of cross neutralization does not lend itself to the antigenic analysis of allergens. It does offer a means of determining the relative strengths of the various reagins in a serum or in two comparable sera.

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AN EXPERIMENTAL STUDY OF THE EFFECT OF ALCOHOL AND ALCOHOLIC BEVERAGES ON ALLERGIC REACTIONS

SUSAN C. DEES, M.D., F.A.C.A.
Durham, North Carolina

CLINICIANS have long been aware that in an occasional person the ingestion of alcoholic beverages may be followed by one of the recognized allergic conditions, such as asthma, urticaria, angioneurotic edema, eczema, or vasomotor rhinitis. The literature contains brief or casual reference to many such patients.[3,4,9,10,11] In some, the symptoms are produced by any or all types of alcoholic beverages; in other instances the reaction is specific for certain beverages or even brands of beverages.[7] Even more frequently the converse has been noted; a few ounces of whiskey, for example, may be a most effective means of relieving or aborting an asthmatic attack. Recent reports by Brown and others have discussed the effectiveness of intravenous alcohol in treating status asthmaticus.[1]

In an attempt to approach this problem of allergy to alcoholic beverages, several questions may be posed: (1) Are individuals sensitive to pure alcohol? (2) Are the symptoms experienced by some persons after drinking alcoholic beverages the result of the effect of the alcohol itself, or due to an allergic reaction to alcohol-soluble protein present in the beverage? (3) Does the alcoholic beverage simply enhance an allergic reaction already existing in the person?

A study of the role of alcohol in the production of clinical allergic reactions is a complex problem, in which factors other than the allergen-antibody reaction are involved. It seemed wise to approach the problem by first considering the effect of alcohol on skin reactivity, using the skin reactions merely as an indicator of an allergic reaction.

The first experiment was done to learn whether the ingestion of alcohol or whiskey would, in itself, alter the size of direct or passive transfer skin reactions. Four groups of subjects were used, nonallergic abstainers, nonallergic drinkers, allergic abstainers and allergic drinkers. The allergic drinkers had never noted any change in their symptoms following the use of alcoholic beverages. The method of study used was to observe the size of both direct and passive transfer skin reactions before and after the subject had taken either grain alcohol or a whiskey* blend. Serum for passive transfer tests was obtained from six drinkers, three allergic and three nonallergic persons. The recipients used were nonallergic abstainers whose skin accepted passive transfer tests. All individuals used were subjected to preliminary skin tests several days before the passive transfer

From the Department of Pediatrics, Duke Hospital and Duke University School of Medicine, Durham, N. C., with the technical assistance of Mr. R. J. Grantham, B.S.
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*Joseph E. Seagram and Sons, Inc., supplied the grain alcohol and V. O. whiskey used in these studies, and also furnished chemical analysis of the latter.

experiment. All tests in the nonallergic persons were negative, except for one slight reaction to dust in one recipient. The extracts used for testing

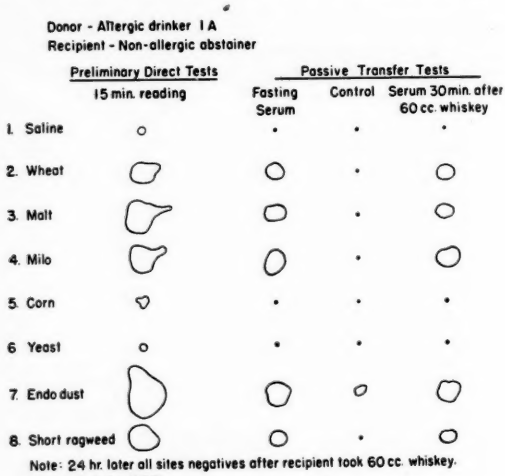

Fig. 1. Direct intradermal tests and passive transfer tests in allergic drinker 1 A. Serum for passive transfer tests obtained fasting and thirty minutes after donor drank 60 c.c. whiskey.

were as follows: wheat 1:1,000 (total N, 50.4 mg. per cent), malt 1:1,000 (25.5 mg. per cent), milo 1:1,000 (20.1 mg. per cent), corn 1:100, Brewer's yeast 1:1,000, Endo purified house dust 1:1,000, short ragweed 1:1,000. A saline control was used for all skin tests. Venous blood alcohol levels were determined by the method of Friedeman and Klaas[2] in the first three experiments, and by the method described by Newman[5] in the fourth.

The results of tests in three allergic donors are shown in Figures 1, 2 and 3. From donors who had been fasting at least twelve hours, blood was drawn both before and thirty minutes after they drank 60 c.c. of a blended whiskey.† A blood alcohol level was obtained with the second specimen. After the usual precautions the serum was injected into the recipient. Forty-eight hours later these sites were tested with the seven extracts. No detectable difference was noted between the passive transfer reactions of the serum obtained before or after the donor drank whiskey. The following morning, with the recipient fasting twelve hours, he, in turn, drank 60 c.c. of whiskey. Blood alcohol levels were obtained thirty minutes later. There were no reactions in any of the passive transfer sites in any recipient after the ingestion of whiskey. No appreciable differences were noted between blood alcohol levels of allergic or nonallergic drinkers. From these preliminary tests we conclude that 60 c.c. of whiskey does not

†Seagram's V.O.

affect the amount of circulating reagin, as demonstrated by indentical passive transfer reactions in serum obtained before, and thirty minutes

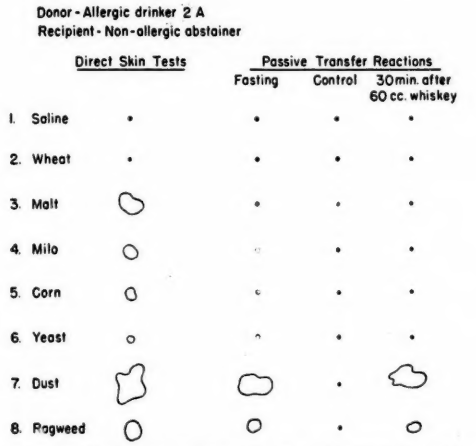

Fig. 2. Direct intradermal tests and passive transfer tests in allergic drinker 2 A. Serum for passive transfer tests obtained fasting and thirty minutes after donor drank 60 c.c. whiskey.

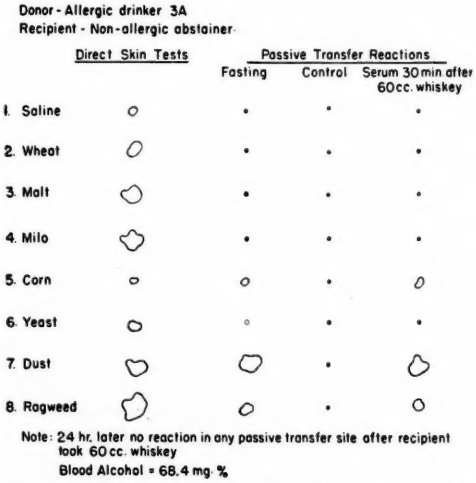

Fig. 3. Direct intradermal tests and passive transfer tests in allergic drinker 3 A. Serum for passive transfer tests obtained fasting and thirty minutes after donor drank 60 c.c. whiskey.

after, the donor drank whiskey. Also, an insufficient amount ot antigen was absorbed enterally by the recipient from 60 c.c. of whiskey to cause

any specific reaction in sensitized sites, or any nonspecific reaction from vasodilatation.

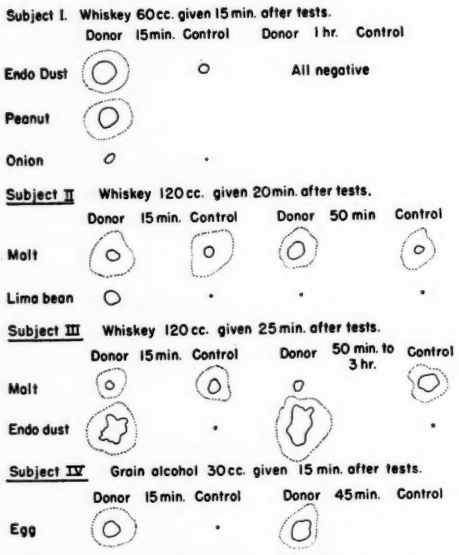

Fig. 4. Passive transfer reactions in allergic sera before and after recipient drank 60 c.c. whiskey or grain alcohol.

The second experiment was an attempt to learn whether alcohol ingested by the fasting recipient at the peak of the skin reaction would in any way affect the skin reaction. These results are summarized in Figure 4.

The serum donors in this experiment were patients extremely sensitive to various foods clinically and by skin tests. When the skin reactions in the passive transfer sites had reached a maximum in ten to twenty minutes after the allergens were injected, the recipient was given whiskey. The first one took 60 c.c. of whiskey. The skin reaction persisted unchanged for forty-five minutes. The second recipient took two 60 c.c. portions of whiskey in twenty minutes, beginning twelve minutes after the sites were tested. All the sites except malt faded in thirty minutes. This persisted unchanged or perhaps with slight increase in size for two hours. In the third subject, again two 60 c.c. drinks of whiskey were taken immediately after the skin reactions had reached their maximum. Two sites, malt and dust, steadily increased in size for two hours. The control site malt in the recipient became larger than it was originally or than the passive transfer site for malt. The reaction did not begin to fade for three hours, a longer time than any skin test had ever lasted in this recipient. The fourth recipient was tested only for egg, then given 30 c.c. of grain alcohol immediately after the fifteen-minute reading, with the wheal just beginning to fade.

Thirty minutes later, or forty-five minutes after the test was started, the wheal had increased slightly in size, the area of erythema was larger.

In these four sera there was an apparent increase in the allergic whealing reaction, for the substances to which the donor was most sensitive, after the recipient ingested alcohol. Also, in two recipients whose control tests were positive for malt, the reactions were similarly prolonged, and in one, apparently increased in size over the original fasting test. The other areas which had shown a little whealing or transient erythema were unaltered by the recipient's ingestion of alcohol and faded in the usual length of time.

TABLE I. CLINICAL AND SKIN REACTIONS IN SUBJECTS HAVING ALLERGIC SYMPTOMS AFTER INGESTION OF ALCOHOLIC BEVERAGES.

Pt. No.	Sex	Age	Symptoms	Agent	Direct Skin tests	Passive Transfer tests	Effect of Alcohol	Blood Alcohol %
H I	M	26	asthma	whiskey gin sherry	corn, oats rice, dust ragweed, yeast	corn, yeast dust, ragweed	increased corn, dust (p. transfer)	
S2	F	57	asthma abd. pain	bourbon whiskey	corn	corn, yeast dust	p. transfers no change	
D3	M	27	urticaria oedema	whiskey	egg, pork	egg	increased p. transfer tests	
G4	F	21	urticaria oedema	whiskey	wheat, milk, dust egg, ragweed		direct tests increased	44 mg.
B5	F	36	asthma	whiskey occasionally	dust, ragweed egg, milk, malt milo, corn zein wheat gliadin	malt, dust corn zein wheat gliadin ragweed	increased direct no change in p. transfers	64 mg.
Wm.6	M	49	histamine headache	beer only	negative	negative	negative	
W.W.7	M	36	oedema	whiskey	negative. histamine positive	negative	histamine wheal increased.	

In the third experiment, seven allergic adults who had had allergic reactions after drinking alcoholic beverages were studied. In the first patient, asthma followed drinking any type of whiskey, gin or sherry. In the second, asthma and severe abdominal pain were produced only by bourbon whiskey. All other types of alcoholic beverage were taken without symptoms. In the third patient, chronic urticaria of six months' duration became very severe and was complicated by angioneurotic edema after drinking any type of whiskey. The fourth person experienced urticaria and edema of the throat and tongue, on occasions so severe as to produce respiratory embarrassment, after drinking whiskey. A fifth had occasional asthma after drinking whiskey. The sixth had histamine headaches, regularly produced by drinking beer. The seventh had angioneurotic edema after drinking whiskey. The symptoms, skin reactions and affect of alcohol on the skin reactions are shown in Table I. Two of the persons studied had blood alcohol levels of 44 to 64 mg. per cent thirty minutes after taking 75 c.c. of a whiskey blend.

Table I shows that in patients No. 1 and No. 3 the passive transfer sites

flared after the recipient drank whiskey; in No. 2 there was no reaction in passive transfer sites. In two patients, No. 4 and No. 5, the direct reaction increased in size after whiskey. There was no change in the passive

TABLE II. RESULTS OF DIRECT SKIN TESTS WITH SIMULTANEOUS BLOOD ALCOHOL LEVELS PERFORMED ON NONALLERGIC SUBJECTS

Non-Allergic Subjects			Skin Tests		Amount Alcohol		Blood Alcohol	Time
No.	Init.		Fasting	After alcohol	cc/Kg	Total vol. cc.	Mgm.%	Minutes
1	C	A	Neg.	Neg.	0.66	45	56	30
2	M	D	Neg.	Neg.	0.75	55	66	30
3	H	A	Neg.	Neg.	0.75	40	60	30
4	E	D	Neg.	Neg.	0.75	60	56	30
5	W	D	Neg.	Neg.	0.75	55	77	30
6	F	A	Pos.	Sl. inc.	0.75	55	61	30
7	S	A	Pos.	Neg.	0.64	120*	48	48
8	B	D	1)Pos.	Same	0.75	66	83	30
			2)Pos.	Same-decr.	0.61	120*	54	30

A = Abstainer
B = Drinker
* = Seagram's V.O. Whiskey

TABLE III. RESULTS OF DIRECT SKIN TESTS WITH SIMULTANEOUS BLOOD ALCOHOL LEVELS PERFORMED ON ALLERGIC SUBJECTS

			Skin Tests		Amount	Alcohol Total	Blood Alcohol	Time
No.	Init.		Fasting	After alcohol	cc/Kg	vol. cc.	Mgm.%	Minutes
1	MH	A	Pos.	Sl. decr.	0.57	75*	60	50
2	JH	A	1)Pos.	Incr.	0.72	120*	63	49
			2)Pos.	Incr.	0.75	55	49	30
			3)Pos.	Incr.	0.72	120*	50	31
			Pos.	Incr.	–	–	63	47
3	W	D	Pos.	Sl. incr.	0.75	55	45	30
4	G	D	Pos.	Incr.	0.55	75*	44	43
5	B	A	1)Pos.	Incr.	0.55	75*	64	41
			2)Pos.	Same**	0.55	75*	73	35
			Pos.	Incr.	–	–	69	50

A = Abstainer
D = Drinker
* = Seagram's V.O. Whiskey
** = Patient received 50 mg. benadryl prior to tests.

transfer sites in No. 5. In subject No. 6, while drinking two bottles of beer provoked a typical headache, skin test sites showed no reaction. An intradermal test to histamine increased in size after drinking alcohol.

The ingestion of alcoholic beverages in this group of clinically "alcohol-sensitive" persons had the same effect on positive skin tests, when

demonstrable, as in the previous group of allergic persons without any clinical sensitivity to alcoholic beverages.

A fourth experiment was done to determine whether any relationship

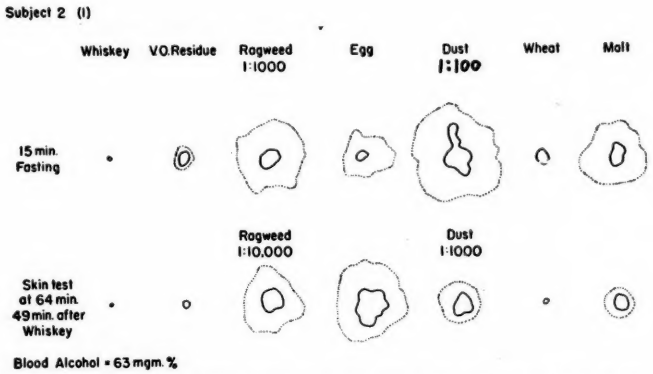

Fig. 5. Comparison of skin reactions before and after drinking whiskey in allergic subject, not sensitive to alcohol. See Table III, Subject 2 (I). Fasting dust, 1:100.

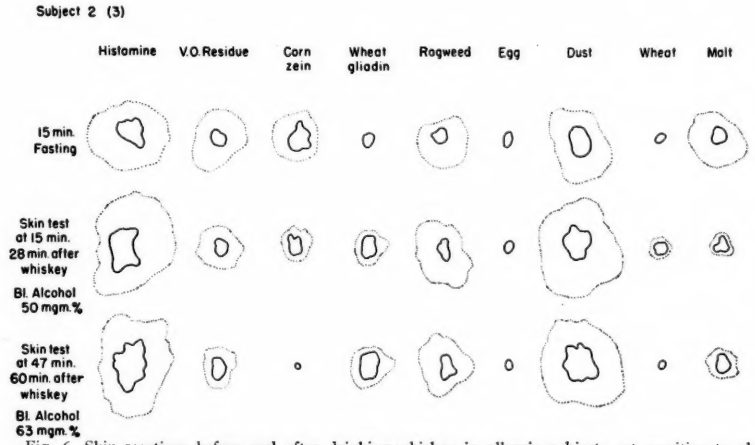

Fig. 6. Skin reactions before and after drinking whiskey in allergic subject, not sensitive to alcohol. See Table III, Subject 2 (3). All extracts same concentration.

exists between the height of blood alcohol level and the size of the skin reaction in both allergic and nonallergic subjects. In this experiment a series of skin tests were done on five allergic and eight nonallergic subjects. Among the eight persons with no personal or family history of allergy, two gave positive skin tests to one or more extracts. The subjects were given grain alcohol or equivalent portions of whiskey blend, in amounts varying from 0.55 c.c. to 0.75 c.c. of 95 per cent alcohol per

kilogram of body weight. Blood alcohol levels were determined at periods ranging from thirty to fifty minutes after the ingestion of alcohol. These varied from a low of 44 mg. per cent to high of 83 mg. per cent. The fasting skin test reading was made at the peak of the reaction, which occurred in fifteen to twenty minutes in all subjects. In some subjects the alcohol was given immediately after the maximum skin reaction was reached, in others the tests were done and recorded on one day, repeated the next day with the alcohol following immediately after the injection of allergen. The results recorded after alcohol are readings made simultaneously on withdrawal of blood for alcohol level. The results are shown in Tables II and III. The skin tests are detailed in Figures 5 through 8 for allergic Subjects 2 and 5 of Table III. These may be summarized by saying that ingestion of alcohol seemed to intensify most of the truly positive skin reactions, as well as the histamine reaction, in the allergic subjects. It had no effect on the very slight reactions or on the negative reactions in nonallergic persons. There was no correlation between the blood alcohol levels and the size of the skin tests. No difference could be observed in height of blood alcohol levels or skin reactions, when whiskey or grain alcohol, in equivalent amounts of alcohol per kilogram body weight, were ingested. It was impossible to predict the blood alcohol level for a given subject, from a measured amount of alcohol or whiskey, as the levels were variable. All subjects were skin tested to a whiskey blend 1:10, and to vacuum distillate residue of the whiskey blend 1:10. The only positive reactions to whiskey occurred in three allergic and in one nonallergic subject who, however, was skin-test-sensitive to several extracts; these gave small positive tests to V.O. residue. In fifteen minutes fasting, 30 minutes after alcohol ingestion, these reactions were increased in size. These reactions did not passively transfer. Two of the allergic subjects who reacted to residue were tested to dilutions of the alcohol soluble cereal protein.** Positive direct reactions were present to corn zein, and wheat gliadin in both patients. Rice bran globulin was negative. The positive tests increased in size after the subject was given whiskey.

DISCUSSION

Various explanations of clinical allergy to alcoholic beverages have been proposed. Tuft[9] suggests that urticaria, in particular, may be the result of the ability of alcohol to dissolve products of protein decomposition in the gastrointestinal tract, with the resulting rapid absorption of these products. In other instances it is possible that various substances from which the brew is made, or which are used in its manufacture, are the responsible allergens. Storm van Leewen,[7] in studying a patient sensitive to a certain brand of champagne, found that the brand which caused symptoms was made from only one variety of grapes whose juice contained

**These purified proteins were very kindly furnished by Dr. D. Breese Jones of the Bureau of Plant Industry, U. S. Department of Agriculture.

both mold and yeast, whereas brands tolerated without symptoms contained only mold. While this patient gave positive skin tests to grape, he was skin sensitive to only the one type of champagne grape mash. Van Leewen

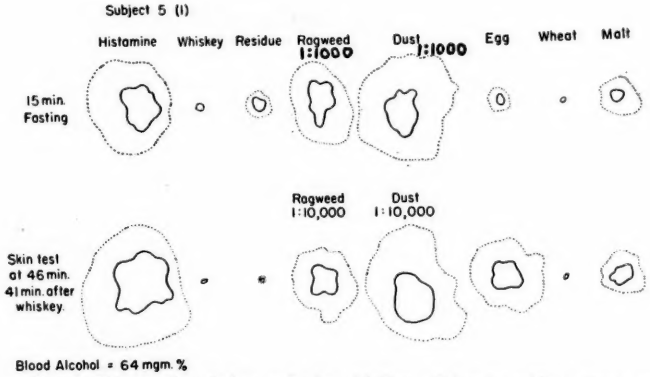

Fig. 7. Skin reactions before and after drinking whiskey in subject allergic to whiskey. See Table III, Subject 5 (1). Fasting dust and ragweed, 1:1,000.

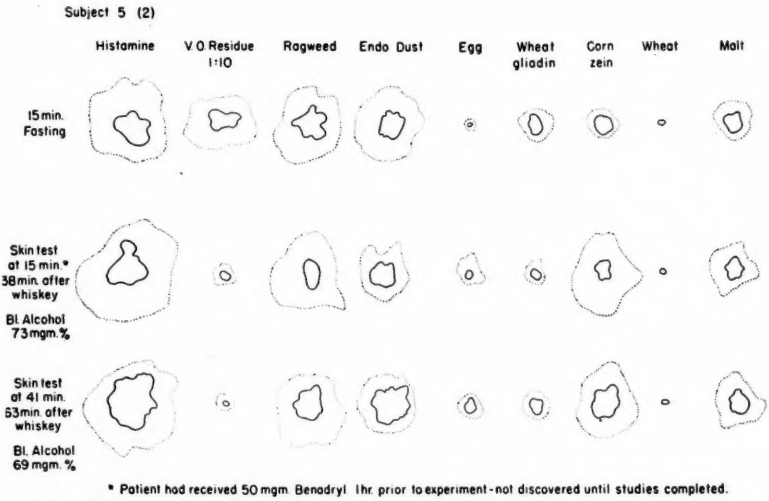

Fig. 8. Skin reactions before and after drinking whiskey in subject allergic to whiskey. See Table III, Subject 5 (2). All extracts same concentration.

suggests that the allergy in this person was actually based on fungus sensitivity.

Studies on gouty patients done by Widal and Joltrain[12] showed a high percentage of positive skin reactions to burgundy wines, with much lower incidence in normal controls. In several fasting gouty patients, a hemo-

clastic crisis was produced by drinking burgundy wine, while no reaction was produced by other types of wine.

Spillman and Lavergne[6] described a person sensitive only to one type of white wine in which albumen was used for clarifying. With this wine extract they were able to sensitize guinea pigs and produce fatal anaphylactic shock. They assume that here the alcohol acts only as a carrier of allergen.

In studying sensitivity to distilled alcoholic beverages the problem is simplified in one respect, since fungi are unlikely sources of allergenic activity. However, whiskey, as consumed by the average drinker, is made from several cereals, whose proportions vary with different batches of even the same brand. White potato and other fermentable substances are also used as sources for neutral spirits. After distillation, various coloring matters and even small amounts of wine, such as sherry, are added to improve palatability.

In the preliminary studies presented here, the ingestion of either grain alcohol or whiskey apparently increases the allergic wheal in size, intensity and duration, regardless of the subjects' clinical sensitivity to alcoholic beverages. This effect is not related to the absolute blood alcohol level, since levels at which positive reactions were enhanced did not result in negative sites becoming positive.

In no instance was a true Prausnitz-Küstner reaction obtained in allergic patients' serum, even in patients who had clinical sensitivity to whiskey. However, the recipients' ingestion of alcohol increased already present passive transfer reactions produced by injection of allergen into sensitized skin sites.

The residue of whiskey was capable of producing positive skin tests in three persons, two of whom had symptoms after taking whiskey and in one who, while not admittedly allergic, gave positive skin reactions to various things and was a moderate drinker.

We can only conclude from the studies of the effect of alcohol on skin reactions that allergic and histamine wheals are increased after ingestion of alcohol. It might be inferred from this that in so-called alcohol-sensitive persons the ingestion of alcohol merely brings to a clinical level a subclinical allergic reaction. This same mechanism, for example, could make food, or inhalant allergens which were unrelated to the contents of the brew, potent enough to cause trouble, or the alcoholic medium could enhance the small quantities of allergens which it contained to a level sufficient to produce an allergic reaction. The means by which alcoholic beverages can act to intensify or produce allergic reactions is somewhat easier to explain than the mechanism whereby alcohol can decrease them. Further studies are necessary for adequate explanation of the marked and specific sensitivity which some persons exhibit toward certain alcoholic beverages.

(Continued on Page 300)

THE ROLE OF ALLERGY IN RHEUMATOID ARTHRITIS AND A SUGGESTED TREATMENT

Preliminary Report

GEORGE E. ROCKWELL, M.D., F.A.C.A.
Milford, Ohio

RHEUMATOID arthritis is essentially caused by a reduction of the blood supply to the tissues, produced by a constriction of the finer vessels of the capillary beds. This vascular nature of the disease may be revealed by various clinical and experimental approaches. In the arthritic patient, for example, one finds a decreased sugar tolerance,[12,19,20,21] which is due not to the decreased ability of the patient to metabolize the carbohydrate, but to a diminished circulation in his tissues. Thus, because the tissues are not adequately supplied with blood, the glucose is not oxidized as rapidly as normally. This has been demonstrated experimentally by decreasing the circulation in the limbs by means of a tourniquet. The vascular nature of the disease is also revealed by a decrease in oxygen consumption and in the rate of absorption from the intestinal tract.[4,10,22,30] Impairment of the capillary circulation can be demonstrated by direct observation of the capillary bed at the cuticles of the arthritic patient's nails[15,16] or in the vessels of the rabbit during the anaphylactic reaction,[1] by comparison of the surface temperature of the arthritic patient with that of the normal individual,[14,32] by the character of the red cell count at the periphery,[5,18] and by the production of arthritis by means of experimentally interfering with the blood supply.[9]

All these studies point to the impairment of the capillary circulation as the predominating pathological finding in rheumatoid arthritis. However, the cause of these changes is not necessarily allergic in nature. What evidence is there then that rheumatoid arthritis is an allergic disease? There is almost daily evidence. Physicians everywhere are obtaining penicillin reactions, many of which are in the nature of arthritic changes that are exactly the same as those found in acute arthritis. Some may question this interpretation of rheumatoid arthritis on the ground that in no instance has a heart condition resulted from an allergic reaction, but, experimentally, heart conditions have been produced and, clinically, cardiographic evidence of heart changes has been obtained in allergic shock.[3] Also, in experimental studies an animal does not receive daily shocks over long periods of time, as does the rheumatic fever patient. Before the advent of penicillin, acute arthritis was frequently associated with serum reactions. This, again, is now accepted as an allergic mechanism. Zinsser[33,34] and others[2,6,7,11,24,25,27,28,31] have felt that rheumatic fever, arthritis, and allied diseases are the result of bacterial or other allergies, and have produced experimental evidence to support their view. The majority of arthritic patients have an amazing amount of personal and/or family history of allergy. Finally, if

the treatment is directed toward this basic cause, vascular allergy, the clinical results are most gratifying.

TREATMENT

Intravenous Histamine.—This is given by a method of Prince's[23] which differs from that of Horton's,[13,29] since with the latter's method the dosage is controlled so as to prevent generalized flushing, whereas Prince advocates, when treating serum sickness and drug reactions, larger and increasing doses of histamine, if necessary, to produce as much as possible a continuous flush without producing a headache. At first the equivalent of 1 mg. of histamine base, usually histamine diphosphate, is placed in 250 c.c. of isotonic saline solution and given intravenously at such a rate as to produce flushing of the face, arms and chest, but not to produce headache. Patients vary in their tolerance of histamine administered intravenously. Therefore, the flow is regulated accordingly so that a patient receives 250 c.c. intravenously in two hours. For example, if 1 mg. of histamine base can be given so as to produce a generalized flush without headache in less than two hours, the dose is increased so that it takes two hours to administer and maintain a continuous flush. The dose is thus adjusted for each patient. This procedure is repeated daily for a week or more, depending on the case, and then two to three times weekly. The treatments are continued for at least six months for mild cases, a year or more for moderate cases, and, if necessary, several years for severe cases. The patient should have food in the stomach just before taking an injection. The dosage prescribed is for adults. We have not had any experience in the treatment of children with this method. The intravenous injections can be given in the office. If the patient is hospitalized, it is not sufficient merely to order histamine intravenously; it is necessary to outline clearly the above directions.

Prolonged Acting Histamine.—Instead of intravenous injections of histamine, some of our cases have been given subcutaneous injections of a prolonged acting histamine, such as ethyl histamine carbonate.[26] The subcutaneous treatment will give a similar flush to that obtained with the intravenous treatment and will last for about an hour. The only advantage of this method is its simplicity.

Infection.—All foci of infection are looked for and eliminated if possible. Also, the infected areas are cultured—the upper respiratory tract, infected teeth, gall bladder, prostate, and other foci of infection.

Bacterial Desensitization.—Either an autogenous vaccine or a stock vaccine, in case the autogenous vaccine is not available, is used for this purpose. Desensitization should be done by the intravenous method. The vaccine should be given intravenously once a week regardless of the method

used in administering the histamine. The initial dose is from 10,000 to 50,000 organisms, and this is gradually increased, depending upon the reaction and the comfort of the patient. The vaccine should not be given more than once a week and should not be started until the patient has had three weeks of histamine therapy. Although we have not used it, the method of Nantz and Blatt[17] for determining bacterial hypersensitivity might be advantageous when selecting the vaccine.

Diet.—Dietetic treatment of rheumatoid arthritis has had varying results. However, the concensus is that if the diet is reduced, the patient is benefited.[8] It is doubtful whether all cases of arthritis are the result of a bacterial allergy. Undoubtedly, in some cases food sensitivity is a contributing cause. Occasionally an arthritic patient shows a definite skin reaction to foods, but this is relatively uncommon. The dietary regime of arthritic patients requires further studies. An elimination diet is generally used, eliminating eggs, milk, wheat, chocolate, peas, beans, and the citric fruits. If the patient improves, the addition of one of these prohibitive foods is added to the diet at intervals.

Medication.—At first aspirin is given for pain but is withdrawn as the latter disappears, which is usually early. Other medications are not used, with the exception of iron orally and liver injections where there is marked anemia. (Lilly's Purified Liver Extract gives less side reactions than the crude liver extract.)

CLINICAL RESULTS

In the series of fifteen cases (all adults), only two patients have not been benefited. One, a woman, sixty-two years of age, had ankylosed joints but no pain or swelling. The other patient, although she has shown no improvement clinically or in her blood sedimentation rate, insists she feels better under treatment.

The remaining thirteen cases showed improvement, some more than others. A summary of the results of the treatment of these thirteen cases follows:

Pain.—Pain usually disappeared during intravenous therapy. Freedom from pain between treatments depended upon the length of time that the patient had been receiving treatment. Usually, the pain was markedly reduced in one week and was almost entirely absent in six weeks.

Aggravation Caused by Weather Change.—Following treatment for three or more months, most of the patients suffered little from weather changes, whereas previously they could predict weather changes as regularly as a barometer.

Swelling.—There was considerable subsidence of swelling the first week, and it was usually absent in three to six weeks.

Range of Motion.—This was increased 10 to 25 per cent in three weeks and 50 to 100 per cent in three to six months.

Blood Count.—The blood count returned to normal in three to six months.

Blood Sedimentation Rate.—The blood sedimentation rate as a rule diminished in three weeks and returned to normal in three to six months.

Relapse.—If treatment was abandoned too early or if the interval between treatments was lengthened unnecessarily, a relapse occurred. The intervals should be sufficiently long to prevent the return of symptoms between treatments, in order that progress may be as steady as possible. Also, it would seem that the main length of treatment should be at least six months, and in many cases, one to two years. None of the patients have been under treatment for as long as two years, so that the question as to the length of treatment is still an open one.

COMMENTS

With the report of this small series of fifteen cases, it is realized that for statistical purposes the number of cases is inadequate and that final conclusions cannot be reached until a larger number of cases have been observed over a longer period of time. Unfortunately, arthritic patients do not consult the allergist first. Our cases are reported at the present time in an effort to stimulate other allergists to become interested in this approach to arthritis therapy. Only through the co-operative and concerted effort on the part of many allergists in trying out this method can the procedure be given its proper evaluation.

SUMMARY

The impairment of capillary circulation by a constricted capillary bed is the predominating pathological finding in rheumatoid arthritis. This vascular change is due to a vascular allergy, toward which treatment has been directed. This has consisted of administering histamine intravenously or a prolonged-acting histamine derivative subcutaneously, together with bacterial desensitization and elimination of offending foods. The clinical results have been gratifying.

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RHEUMATOID ARTHRITIS—FOOD ALLERGY AS A FACTOR

MICHAEL ZELLER, F.A.C.P., F.A.C.A.
Chicago, Illinois

THE ETIOLOGY of rheumatoid arthritis is still unknown. Many theories have been advanced, the most acceptable being the hypothesis of bacterial allergy, in which it is assumed that a sensitivity is developed to bacteria or their products. Although the idea of bacterial allergy has been accepted by some for many years, the possibility of food allergy as a factor in the production of rheumatoid arthritis has received little or no consideration. In fact, rheumatologists not only discount food allergy in rheumatoid arthritis, but frown at the mention of such a possibility. An example of this attitude is expressed in the 1941 review on arthritis,[3] in which it is stated that "the arthritis of serum sickness is the only type of arthritis that can be classified as anaphylactic or allergic in nature." It is stated further that "the absence of a single article under the title 'allergic arthritis' in the American or English literature of 1940 rings a note of encouragement." The authors of this article dispute also the validity of several reports of intermittent hydrarthrosis definitely established as being due to food allergy. It is natural, then, that in view of such an attitude on the part of the profession in general that one approaches this subject with extreme caution.

Various forms of arthritis and myalgias have been described as being due to food allergy. Solis Cohen,[11] in 1914, reported twenty-seven cases of angioneural arthrosis in which painful swelling of joints occurred at various intervals, but with freedom from pain between attacks. Kahlmeter,[5] in 1939, described similar cases under the term "allergic rheumatism," and in 1941 Hench and Rosenberg[2] used the new name of "Palindromic rheumatism" in a group of thirty-four cases characterized by oft-recurring, afebrile attacks of acute arthritis and periarthritis generally involving only one joint, but at times multiple joints. In the latter group of cases, an allergic hypothesis was considered as a possibility in the etiology. Rowe[9] mentions food allergy as a factor in rheumatoid arthritis and, with Randolph,[7] ascribes various muscular aches and pains to food allergy. Intermittent hydrarthrosis due to foods has been described by Taub and Lewin[6] in 1936, by Service in 1937,[10] and by Berger[1] in 1939. In 1924 and again in 1944, Turnbull[13,14] reported relief of rheumatoid arthritis by food exclusions. Vaughan, in 1943, reported twenty-seven cases of recurrent or chronic joint symptoms, thirteen of which he classified as rheumatoid arthritis due to food allergy.

It might be pertinent to mention that there is an analogy between the clinical course of rheumatoid arthritis and the most classical manifestation of allergy, that is, bronchial asthma. Rheumatic patients reveal from two

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to three times as much allergy as a similar group of controls. Both rheumatoid arthritis and bronchial asthma are chronic diseases subject to remissions and exacerbations. They may show spontaneous recovery for as long as ten years and then suddenly recur, or they may progress rapidly to produce complete disability because of irreversible changes. Both diseases frequently remain stationary, or they may gradually improve to complete recovery. The effect of jaundice and pregnancy in producing relief of many cases of bronchial asthma and rheumatoid arthritis is an established fact, and particularly interesting are the case reports describing complete reversibility of ankylosed joints due to jaundice. Jaundice has also produced remissions from migraine, ragweed hay fever, and egg sensitivity. Hench very properly raises the question whether hepatitis and jaundice are anti-allergic. Both bronchial asthma and rheumatoid arthritis are often temporarily relieved by fever therapy such as is produced by typhoid vaccine. Finally, both diseases have as a prominent feature edema and eosinophilic infiltration.[12]

The question of the sedimentation rate which is highly regarded by some as an index of arthritic activity may be singled out as an important dissimilarity between bronchial asthma and rheumatoid arthritis, but this difference is more apparent than real. Uncomplicated allergic diseases, in general, present normal or even lessened sedimentation rates, but many so-called infectious asthmas reveal increased sedimentation rates due presumably to the complicating infection. In the arthritis review[4] of January 1948, considerable question is raised as to the accuracy of the sedimentation rate in rheumatoid arthritis, pointing out that in one series of early or mild cases rates were normal in 50 per cent. In other patients with "hot swollen joints" sedimentation rates were normal, and in still others with clinically inactive stages of the disease the rates were increased. The inaccuracies of the test, therefore, led to the conclusion that clinical evaluation was much more valuable than the sedimentation rate, both in diagnosis and following the course of rheumatoid arthritis.

In view of the capricious nature of rheumatoid arthritis, it becomes imperative to exert every precaution in evaluating any therapeutic measure, particularly a new or freshly revived old treatment. The factor of suggestion associated with any therapy in itself, together with the changing nature of this disease, has often been effective in producing apparent cures or improvements. Our approach to rheumatoid arthritis from the viewpoint of food allergy is made, therefore, with complete cognizance of the dangers and pitfalls inherent in the procedure.

Our criteria in establishing the diagnosis of the disease rested on symptoms of fatigue, exhaustion, low-grade fever developing acutely or gradually, and associated with pain, redness and swelling usually of symmetrical joints, fusiform enlargement and spindle-shape fingers, muscular atrophy, glossy skin, clammy hands, contractures and deformities occurring as a whole or in part.

Our procedure of study consisted of the usual allergic history taking, which we found valuable in that foods that were productive of other allergic symptoms often also cause arthritic symptoms. In no instance, however, was the patient certain or even particularly suspicious of any one food as a cause of symptoms such as is often encountered in asthma or vasomotor rhinitis. Some felt that foods, in general, produced symptoms but were unable to specify which were causative. Skin tests, both scratch and intradermal, were of relatively little value, although positive skin responses to allergens producing associated allergic symptoms, such as hay fever or rhinitis, were usually present. The most direct and effective diagnostic measure consisted of food ingestion tests combined with white blood cell responses, according to the technique described by Rinkel.[8] The following case reports illustrate our approach:

Case 1.—A white woman, aged thirty-nine, was seen first in May, 1946, for complaints of headaches every two to three weeks all her life, constipation since childhood, nasal congestion and sneezing for several years. Nine years ago she noticed a gradual onset of fatigue and vague aches and pains of her hands, wrists and later of the shoulders and knees, which seemed to be worse with changes in weather. Gradually, her symptoms increased and she began to note swelling of the proximal finger joints associated with much pain and limitation of motion. This appeared in attacks often co-incident with low-grade fever and mild sore throat. Various therapeutic measures, including stock and autogenous vaccines, vitamins, baths and medications were ineffective in arresting the process. Coal tar products and rest produced partial relief. She had observed that milk ingestion produced diarrhea and that chocolate and bananas resulted in headache. Her two sons have ragweed hay fever and her father had asthma.

Examination revealed, essentially, congestion of the nasal mucous membranes with some clear mucous discharge. The proximal joints of the fingers of both hands were diffusely swollen, tender, and on movement produced considerable pain. The skin was somewhat glossy and the fingers in general had a spindly appearance. Scratch tests were negative throughout, and intradermal tests likewise were negligible, except for slight reactions to chocolate, pork, potato, house dust and cat hair. There was an eosinophilia of 3 per cent and a sedimentation rate of 20 mm. in one hour (Westergren). Ingestion tests with milk resulted in nausea, diarrhea, and headache, and a fall in leukocyte count from 7,400 cells to 5,400 cells. In one hour a gradual onset of pain in the fingers and shoulders developed, accompanied by fatigue which forced the patient to bed. Increased swelling of the fingers was also noted. This increased in intensity for sixteen hours, then gradually subsided in thirty-six hours. Beef, bananas, fish and nuts, on ingestion tests on numerous occasions, resulted in joint symptoms, always starting with fatigue and followed later by swelling and pain in the proximal finger joints. Exclusion of these foods has produced relief of joint symptoms, but at this date ingestion still produces reactions as described. The swelling of the fingers has not completely disappeared, for some of the changes are irreversible. The sedimentation rate is 8 mm. per hour at present.

Case 2.—A man, aged sixty-seven, office worker, complained of pains in the hands, knees and ankles for twenty-five years, the pains coming on gradually and accompanied by fever at times. Frequently, the pain and swelling caused disability for several days at a time. Deformities of the hands and knees caused limited motion, and in recent years he could get about only with the aid of two canes. The fingers presented

a spindle shaped appearance as well as ankylosis of several finger joints. The wrists, knees and ankles were also diffusely swollen and somewhat ankylosed. There was no history of rheumatic fever, hay fever, eczema, or asthma in the patient or his family. He had observed that whiskey and beer produced swelling and pain of the involved joints, starting in a few hours and reaching a peak in sixteen hours, after which they subsided gradually in a day or two.

Every therapeutic measure had been exhausted in attempts to obtain relief. Allergic studies were made partly to satisfy the patient's desire to exclude this factor as a cause of his illness, and partly on the basis of previous encouraging results in the allergic management of this disease. Scratch and intradermal tests were negative throughout. On the basis of ingestion tests, it was determined that wheat, eggs, fish, tomatoes and pork produced swelling and pains in the involved joints from four to six hours after eating. This was accompanied by fatigue, often of sufficient intensity to produce disability for several days. The painful joints attained their maximum intensity usually within sixteen to eighteen hours, after which they subsided. Upon exclusion of the aforesaid foods, the patients symptoms decreased 80 per cent within three months. Reingestion then again produced symptoms, and six months later a similar result was noted. Two years later limited tolerance to these foods had been reached in that ingestion at certain intervals was tolerated without producing symptoms. Meanwhile, much of the deformity had disappeared as well as some of the ankylosis, although some of these changes seem to be irreversible. The sedimentation rate in May, 1946, was 80 mm. in one hour; in September, 1947, 60 mm. in one hour; in December, 1947, 40 mm. in one hour; and in March, 1948, 38 mm. in one hour—all Westergren method.

Case 3.—A white woman, aged forty-one, complained of pain and swelling of the wrist, hand and proximal finger joints of six years' duration, developing gradually. At times weather changes seemed to provoke symptoms, but at other times no relation could be detected. The pain was more or less constant, interspersed with exacerbations of acute swelling and pain of the involved joints, and accompanied by low-grade fever, malaise and sore throat. Gradually, the proximal finger joints developed definite spindle appearance with limitation of motion. Paroxysms of sneezing had been noted for twenty years. These occurred daily, all year, and were not influenced or precipitated by any known factor. Running of the nose was not conspicuous, but nasal congestion was noted at times.

A prominent group of symptoms included abdominal distention, cramps, borborygmi and attacks of diarrhea occurring almost daily. At times the cramps would double up the patient, and the diarrhea would persist throughout the day.

Examination revealed essentially post-pharyngeal, linear streaking and slight greying of the inferior turbinates. During an acute exacerbation of joint swelling, a diffuse redness of throat was observed. On the post-pharyngeal wall, six to eight vesicles measuring 1 to 3 mm. in diameter could be seen. Tonsils had been removed. The chest did not reveal any significant findings. The abdomen was soft and tympanitic. The wrists, hands and proximal finger joints were slightly swollen, with some limitation of motion. During several years' observation, while the patient was being treated with vaccines and other measures, repeated and numerous episodes of pharyngitis were noted with the particular characteristic of pharyngeal vesicle formation already referred to. Later swelling of the knee and shoulder joints caused considerable disability.

Various types of therapy including stock and autogenous vaccines, salicylates, removal of foci of infection, baths, massage, bee venom, and change of climate failed to prevent recurrent attacks of pain and toxicity. Then, partly on the basis of the nasal symptoms, an allergic study was made.

The only significant skin test was to house dust, all others being negative. In-

gestion tests with the most frequently eaten foods were then done. Pork produced no significant cell count change, but borborygmi and nasal congestion resulted in forty to sixty minutes after ingestion.

Ingestion of milk resulted in coughing, gradually increased fatigue, painful joints in forty-five minutes, sore throat with vesicle formation on the post-pharyngeal wall, and slight fever in three hours. Later diarrhea developed, persisting throughout the night. The entire reaction gradually subsided in thirty-six hours. Lettuce, white potatoes, and string beans all produced sore throat, slight fever and joint pains with swelling within three hours, persisting usually from twenty-four to thirty-six hours. Ingestion tests performed with six other foods did not reveal any incompatibility.

The exclusion of these foods from the diet resulted in remarkable improvement. In order to corroborate cause and effect, the foods producing symptoms have been ingested deliberately on repeated occasions either singly or as contained in a meal, and each time fatigue, nasal, throat, joint and gastro-intestinal symptoms followed. The sedimentation rate in this patient at no time revealed significant change beyond normal.

Case 4.—A white woman, aged forty-two, complained of nasal congestion present for ten years, pruritus ani for ten years, headaches for fifteen years, and arthritis of the hands, wrists, knees, and shoulders for twenty years. The arthritis was more or less constant and was thought to be worse before a rain. Fatigue was present in intermittent periods, with occasionally slight fever. Her father has hives, one brother and one sister have atopic eczema, and her mother had angioneurotic edema.

Examination revealed, essentially, paleness and swelling of the nasal mucous membranes. There was a spindle-shape deformity of the fingers of both hands, diffuse swelling of the knees, ankles and elbows, with partial ankylosis of some of the joints. Skin tests did not reveal any significant reactions. Ingestion tests with milk produced sneezing and headaches within twenty minutes, lasting twenty-four hours. The leukocyte count dropped from 5,900 cells to 3,900 cells in forty minutes. Wheat produced sneezing in fifteen minutes, with a drop in the leukocytes from 7,200 to 4,200 cells in forty minutes. Eggs produced nausea in five minutes, with a decrease in the leukocytes from 5,400 to 4,400 in forty minutes.

The patient was placed on a diet which included basic foods to which she reacted compatibly. Various foods were then added to the diet, one at a time at intervals of two days, and the following reactions were determined: Beef resulted in swelling and pain of the hands, shoulder and knee joints between four and five hours and accompanied by fatigue. This persisted for thirty-six hours after which the pains, swelling and fatigue subsided. In the last six months this test has been repeated on three different occasions with the same result. Eggs, pepper and garlic produced vaginal itching and eruption within two hours; pork resulted in rectal itching in two hours. Wheat, after being eliminated for three months, can now be tolerated once a day without nasal symptoms. Ingestion of milk resulted in nasal congestion and is still eliminated from the diet.

It is of interest that this patient had arthritis only from the ingestion of beef, although many other foods caused allergic symptoms other than arthritis. It is also noteworthy that the deformity of the hands which appeared irreversible in the beginning has disappeared to an extent that is barely noticeable at the present time. These case reports are representative of good results and reveal, in our opinion, clear cut relations between cause and effect in establishing food allergy as a factor in rheumatoid arthritis. We use the word factor for it has not been possible to eradicate arthritic symptoms in their entirety inasmuch as slight symptoms recur from time to time, but not of sufficient degree to produce disability or even noticeable discomfort. The degree of symptoms persisting may be due to other food allergies not diagnosed, or to unknown factors.

It should be mentioned that we have also had some poor results in rheumatoid arthritis using techniques identical to those described. Some of these patients have had an associated allergy and some have not. We have been unable to explain our failures except that it is possible that not all rheumatoid arthritis is associated with food allergy as a component in the etiology or it may well be that our diagnostic approach is still too inadequate to establish the food factor in these cases. Inasmuch as some of the cases presented co-existing inhalant allergies, hyposensitizing treatment was given with the involved antigens; but whether this therapy was used or not there was no noticeable effect on the arthritis. We have, tentatively, therefore ruled out inhalant allergies as factors in our results. Vaughan described two cases of arthritis in which inhalants are suggestive factors in the etiology.

An impressive feature is the striking improvement following exclusion of the food antigens exceeding that seen in other allergies. Joints which at first presented completely irreversible changes rapidly show disappearance of swelling and in some instances even deformity clears up. Mention has already been made of the fact that in rheumatoid arthritis this is sometimes seen spontaneously with or without treatment; but the fact that rheumatoid symptoms can be produced repeatedly at will by ingestion of the specific food allergen, differentiates improvement by food exclusions from spontaneous remissions. It is of interest to note that weather changes, which apparently are preceded by joint symptoms in many of these patients, are without effect upon proper food exclusions. Frequently foods which cause arthritis often are productive also of gastro-intestinal or nasal allergic symptoms.

The features favoring food allergy as a factor in rheumatoid arthritis are as follows:

1. The history of foods producing allergic symptoms.
2. The presence of other allergies in the patient.
3. The presence of allergy in the family.
4. The chronicity of joint symptoms with repeated exacerbations at various intervals.
5. The relief of symptoms by proper food exclusions.
6. The production of arthritic symptoms by ingestion of the incriminated foods on repeated occasions.
7. The knowledge that foods produce other allergic symptoms such as gastro-intestinal or nasal symptoms.

The evidence presented fulfills sufficient allergic conditions to establish food allergy as a component in the production of rheumatoid arthritis in some cases. It would be unwise to attribute the entire syndrome to food allergy at this time.

4753 Broadway

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THERAPEUTIC EFFECTS OF CERTAIN ANTIHISTAMINE DRUGS IN ALLERGIC CONDITIONS

Comparative Study

HILBERT L. HARRIS, M.D., F.A.C.A.
Syracuse, New York

THE purpose of this study was to determine the value of certain antihistamine drugs in the amelioration of the symptoms in a variety of allergic conditions. Because of the enthusiasm attendant on the introduction of any new drug, particularly those which have received such widespread publicity as the antihistamine group, it is most difficult for the average physician to determine accurately the actual place of these products in his therapeutic armamentarium. The patients frequently have been made aware of the new "boon to allergy" through the newspapers and radio, as well as through the glowing reports of their friends who have received these new drugs from their physicians. It is to be borne in mind that in dealing with this particular group of patients, i.e., those prone to allergic states, a good percentage of this group are hypersensitive, not only to certain allergens but to suggestion on the part of physicians, friends, et cetera. They are chronically ill people, ever hoping for relief from their sufferings, and anxious to try any measure which may afford relief. One has only to examine the scores of diets, medicines, vitamin preparations, and other measures which have been in vogue in the past, each with its enthusiastic followers and none with the backing of impartial, scientific evaluation, to understand that a tremendous psychic factor must be present in these patients.

Thus, it seemed of prime importance to the writer to attempt to keep these psychic factors in a position of minimum influence, and to try to base an evaluation on as nearly an objective and impartial plane as possible. The writer was fully aware of the difficulties inherent in a study of this nature, and readily grants that the influence of publicity concerning a "new drug" played a part in the patient's reactions. However, it is felt that these factors were of less importance in this study than in some similar attempts, because a definite effort was made to minimize their influence in the evaluation of the results.

Along this line of reasoning, it was thought that the study would be facilitated by having the different drugs employed presented in a similar physical form as to their appearance. Accordingly, nearly all of the drugs used were manufactured as a white, round, compressed tablet, which to the casual observer presented no differentiating features. No prescriptions were issued, the drugs being given to the patient by the physician personally. When one drug was being exchanged for another, an attempt was made to keep the patient unaware of the substitution. No explanation of the nature of the material used, or of its probable effect on the patient, was

given. No warning as to possible side effects that might be expected was made. There was very little emphasis on the fact that a "new drug" was being used to help the patient. Frequently the same drug was prescribed two or more times, with the patient unaware of the change back to a material which he had formerly reported as ineffective or effective, as the case might be. The study was continued for a nine months' period so that sufficient time elapsed to allow such factors as seasonal variations, intercurrent infections, normal variations in emotional status, and menstrual cycle influences to play a repeated part. The patients were selected at random from the private practice of the author and from the Allergy Clinic of the Syracuse Free Dispensary. About 100 individuals were studied. However, because of incomplete observation on many of these cases, only about sixty-five are included in the data presented in this paper. Each patient was seen on every occasion by the writer. A strong attempt was made to encourage the patient to use only one medication at a time. However, in some instances, particularly among the asthmatic cases, certain patients were forced to resort to the use of ephedrine compounds, adrenaline inhalations, et cetera, when they were in marked distress and receiving no apparent benefit from the drug being investigated at that particular time.

The cases came from all walks of life, but were largely from the so-called "middle class." They were of average intelligence and were afflicted with their ailments in moderate degree, all being ambulatory. They were the typical cases which one would encounter in any practice emphasizing allergy in the United States. The majority of the patients observed in this study had been under care for some time prior to this investigation and were being given hyposensitization therapy with various extracts. Throughout the period of observation, while taking antihistamine substances, hyposensitization therapy was continued on these patients at regular intervals, just as it was prior to this period.

MATERIALS

The drugs employed in this study were: Pyribenzamine (Ciba), Histadyl (Lilly), Hydryllin (Searle), Compound 1695 (Searle), Benadryl (Diphenhydramine), (Searle), Aminophyllin (Searle), and a placebo (Searle). The drugs were supplied through the courtesy of the various manufacturers.

Pyribenzamine (tripelennamine HCl ethylenediamine monohydrochloride) was supplied in 50 mg. tablets and employed in doses ranging from 25 to 100 mg. repeated from once to four times over a twenty-four-hour period.

Hydryllin (Searle) is a mixture of 25 mg. of Hydryllin (Diphenhydramine) and 100 mg. Aminophyllin combined in a single tablet. It was employed in doses ranging from one to two tablets, repeated as necessary from one to four times during a twenty-four-hour period.

Compound 1695 (Searle) is described as 8-chlorotheophyllin salt of 10-β-dimethylaminoethyl phenothiazine. It is stated by the manufacturers to be less toxic than Benadryl in animal studies and very effective as an antihistamine agent. The dose employed was one to two tablets taken from one to four times during a twenty-four-hour period.

Histadyl (Lilly) Thenylpyramine Hydrochloride is described by the manufacturers as a potent antihistamine substance with a minimum of side effects. It was employed in doses ranging from 25 to 100 mg. given from one to four times during a twenty-four-hour period.

Diphenhydramine (Searle) is comparable to Benadryl Hydrochloride (Parke-Davis) and was administered in doses ranging from 50 to 100 mg. taken as necessary from one to four times during a twenty-four-hour period.

The placebo requires no further description other than to state that it closely resembled many of the other medications in appearance, and contained no therapeutically active ingredients. It was employed in doses ranging from one to two tablets to be taken as required from one to four times in a twenty-four-hour period.

Aminophyllin tablets containing 125 mg. of the drug were also employed. Here again, the dose was from one to two tablets to be taken as necessary from one to four times during a twenty-four-hour period.

CASES

The cases studied included bronchial asthma, with various causative factors, pollinosis, a few cases of migraine, a few cases of dermatitis of allergic etiology, a small number of cases of urticaria of at least two weeks' duration, and an occasional instance of gastrointestinal allergy, manifested by diarrhea and abdominal cramps.

Table I summarizes the cases according to type, sex, age and duration of complaints.

Table II attempts to indicate the degree of efficacy of the various drugs used as to subjective and objective observation. An attempt is made to list the relationship of known emotional factors in some of these instances. An excellent response was credited numerically with three points. This was interpreted to mean that the patient was practically free from his complaints. A numerical credit of two points was given if the relief obtained was definite but not complete. One point was used to indicate some amelioration of the symptoms, which persisted, however, in lesser intensity. No credit was allowed in equivocal instances.

REACTIONS

In no instance was there a sufficiently severe reaction to cause the writer to feel that these drugs are potentially dangerous to prescribe in the moderate doses employed. In the few instances in which blood counts were

TABLE I

Allergic Manifestation	Sex	Age	Duration of Complaint	Hyposensitization Therapy
Vasomotor Rhinitis	M	27	4 yrs.	Being used
Bronchial Asthma	F	31	2 yrs.	Being used
Pollinosis	F	13	8 yrs.	Being used
Bronchial Asthma	F	15	10 yrs.	Being used
Vasomotor Rhinitis	F	39	15 yrs.	Being used
Bronchial Asthma	F	60	20 yrs.	Being used
Allergic Dermatitis	F	30	3 wks.	Not used
Vasomotor Rhinitis	M	54	25 yrs.	Being used
Vasomotor Rhinitis	M	18	10 yrs.	Being used
Colitis	F	30	6 mos.	Not used
Urticaria	M	22	1 yr.	Not used
Bronchial Asthma	F	43	35 yrs.	Being used
Bronchial Asthma	F	65	20 yrs.	Being used
Urticaria	F	42	2 mos.	Not used
Bronchial Asthma	M	29	1 yr.	Being used
Bronchial Asthma	M	61	5 yrs.	Being used
Pollinosis-Br. Asthma	F	31	4 yrs.	Being used
Bronchial Asthma	M	42	4 yrs.	Being used
Pollinosis-Br. Asthma	M	38	3-6 yrs.	Being used
Vasomotor Rhinitis	M	26	5 yrs.	Being used
Allergic Dermatitis	F	16	1 yr.	Being used
Bronchial Asthma	M	24	3 yrs.	Being used
Pruritis	F	70	4 yrs.	Not used
Vasomotor Rhinitis	M	31	3 yrs.	Being used
Allergic Conjunctivitis	F	26	6 yrs.	Not used
Bronchial Asthma	M	28	5 yrs.	Being used
Bronchial Asthma	M	22	2 yrs.	Being used
Urticaria	M	18	1 yr.	Not used
Pollinosis-Br. Asthma	M	32	4 yrs.	Being used
Vasomotor Rhinitis	F	44	16 yrs.	Being used
Allergic Bronchitis	F	26	1½ yrs.	Being used
Pollinosis-Br. Asthma	F	5	2 yrs.	Being used
Pollinosis-Rhinitis	F	14	6 yrs.	Being used
Eczema-Pollinosis	M	9	4 yrs.	Being used
Vasomotor Rhinitis	F	48	15 yrs.	Being used
Vasomotor Rhinitis	F	22	4 yrs.	Being used
Bronchial Asthma	M	50	2 yrs.	Being used
Pollinosis	M	38	14 yrs.	Being used
Pollinosis	F	27	8 yrs.	Being used
Vasomotor Rhinitis	M	27	5 yrs.	Not used
Vasomotor Rhinitis	F	13	5 yrs.	Being used
Allergic Dermatitis	F	13	10 yrs.	Not used
Pollinosis-Br. Asthma	M	20	5 yrs.	Being used
Migraine	F	31	4 yrs.	Not used
Bronchial Asthma	M	45	10 yrs.	Being used
Pollinosis	M	35	6 yrs.	Being used
Pollinosis	F	23	8 yrs.	Being used
Pollinosis	F	30	15 yrs.	Being used
Bronchial Asthma	M	42	13 yrs.	Not used
Pollinosis	M	28	12 yrs.	Being used
Pollinosis	F	36	12 yrs.	Being used
Vasomotor Rhinitis	F	27	15 yrs.	Not used
Pollinosis	F	43	6 yrs.	Not used
Allergic Bronchitis	M	12	4 yrs.	Being used
Pollinosis	F	21	4 yrs.	Being used
Pollinosis	F	39	12 yrs.	Being used
Bronchial Asthma	M	38	6 yrs.	Being used
Bronchial Asthma	F	23	13 yrs.	Being used
Bronchial Asthma	M	45	5 yrs.	Being used
Bronchial Asthma	M	27	4 yrs.	Being used
Migraine	F	31	16 yrs.	Not used
Urticaria	F	42	1 yr.	Not used
Migraine	M	23	10 yrs.	Not used
Colitis	F	29	1 yr.	Not used
Pollinosis	F	23	8 yrs.	Being used

obtained, there was no significant change in the white count nor any evidence of red cell destruction. The urine was examined on several occasions in certain of these patients, and no significant deviations from normal were observed. In an estimated 10 to 15 per cent of the cases, some drowsiness was reported which was moderate in degree and rarely caused the patient to abandon the drug. About the same number of patients complained of nausea following ingestion of these drugs. Only rarely did this result in emesis. Taking the medications with milk seemed to

TABLE II

Allergic Manifestation	Response to Drugs								Emotional Factors	Type of Relief	
	PBZ	Benadryl	Hydrylin	Comp. 1695	Histadyl	Aminophyllin	Placebo	Ephedrine Compounds, etc.		Objective	Subjective
Pollinosis-Asthma	2	1	1	1	2	0	0	2	Minimal	Very little change	Mostly subjective
Bronchial Asthma	0	0	0	0	0	1	0	2	Minimal	Very little change	No marked effect
Pollinosis-Asthma	2	2	3	3	3	2	1	2	Marked	Marked effect	Marked effect
Vasomotor Rhinitis	2	2	1	2	2	1	0		Minimal	Very little change	Marked effect
Allergic Dermatitis	1	0	1	0	2	0	0		Minimal	Sole basis	
Bronchial Asthma	0	0	1	0	0	1	0	3	Minimal	Sole basis	
Pruritis	2	3	2	2	2	0	1		Moderate		Sole basis
Vasomotor Rhinitis	2	1	1	2		0	0		Minimal	Very little change	Mostly subjective
Allergic Conjunctivitis	3	2	1	2	2	0	2		Marked	Very little change	Mostly subjective
Bronchial Asthma	1	1	3	1		2	0	3	Minimal	Very little change	Mostly subjective
Bronchial Asthma	1	2	2	1		1	1	2	Minimal	Very little change	Mostly subjective
Urticarea	2	2	2	1	2	0	0		Marked	Very little change	Mostly subjective
Pollinosis-Asthma	2	2	1	1	2	2	0	2	Minimal	Moderate effect	Mostly subjective
Vasomotor Rhinitis	3	2	1	1	3	0	1		Marked	Slight improvement	Mostly subjective
Allergic Cough	2	2	1	0		2	1	3	Marked	Slight improvement	Mostly subjective
Pollinosis-Asthma	2	2	2	1		0	0	3	Minimal	Marked effect	
Pollinosis-Rhinitis	3	3	2	3			2		Marked	Marked effect	
Pollinosis-Asthma-Eczema	2	2	2	2	1		2		Marked	Marked effect	Marked effect
Vasomotor Rhinitis	1		2	1	2	0	1		Marked	Variable findings	Mostly subjective
Vasomotor Rhinitis	2	2	1	1		0	1		Minimal	Variable findings	Mostly subjective
Vasomotor Rhinitis	1	1	1	1		0	0		Moderate	No improvement	Mod. improvement
Contact Dermatitis	2	2							Minimal	Def. improvement	Marked improv.
Vasomotor Rhinitis	1	1	1	3		0			Minimal	No def. improv.	Mod. improvement
Pollinosis	3	2	1	1	3	0	0		Minimal	Def. improvement	Marked improv.
Bronchial Asthma	1	1	3	1		2	0	3	Minimal	Slight improvement	Mostly subjective
Pollinosis	3	3	3	3	3	1	1		Moderate	Def. improvement	Marked subjective
Pollinosis	3	3	2	3	3	0	0	2	Minimal	Def. improvement	Marked subjective
Vasomotor Rhinitis and Allergic Cough	0	0	0	0	0	0	0	0	Marked	No improvement	
Vasomotor Rhinitis-Allergic Dermatitis	2	2	2	1	3	1	0		Moderate	No improvement	Marked subjective
Pollinosis-Asthma	2	2	1	1			1		Moderate	Def. improvement	Marked subjective
Migraine-Allergic Cough	2	1	1	1				2	Marked	Cough improved	Mostly subjective
Bronchial Asthma	1	1	2	1		2	0	2	Minimal	Slight improvement	Mostly subjective
Pollinosis	3	3	3	3	3	1	0	2	Minimal	Def. improvement	Marked subjective
Pollinosis	3	3	3	3		0	0		Minimal	Def. improvement	Marked subjective
Pollinosis	2	2	3	2		0	0		Minimal	Def. improvement	Marked subjective
Bronchial Asthma	0	0	1	0	0	1	0	2	Minimal	No improvement	Slight improvement
Pollinosis	3	3	2	2		3			Minimal	Def. improvement	Marked subjective
Pollinosis	3	2	3	2	3	0	1		Moderate	Def. improvement	Marked subjective
Vasomotor Rhinitis	2	2	1	1	2	0	0		Minimal	No improvement	Marked subjective
Pollinosis	2	1	1	0	2	0	0		Minimal	No improvement	Moderate improv.
Allergic Cough	1	1	1	1	1	1	1		Minimal	No improvement	Def. improvement
Pollinosis	2	2	1	3	2		1	2	Minimal	Slight improvement	Def. improvement
Pollinosis	2	2	1	2	3		1	1	Moderate	Slight improvement	Def. improvement
Bronchial Asthma	0	0	0	0	0	1	0	2	Minimal	No improvement	No improvement
Bronchial Asthma	1	1	2	1	1	2	0	3	Minimal	Def. improvement	Mod. improvement
Bronchial Asthma	1	1	1	1	1	2	0	3	Minimal	Def. improvement	Mod. improvement
Asthma & Rhinitis	2		2	1	1	1	0		Minimal	Slight improvement	Mod. improvement
Pollinosis	2	2	1	0					Minimal	No improvement	Mod. improvement

relieve these symptoms in a fair number of patients complaining of gastric disturbances. Other side effects which have been reported in the literature, such as nervousness, et cetera, were not encountered in this series of cases. On the whole, it may be stated that the major side effects seen were drowsiness and nausea. The former complaint frequently diminished as the patient continued to use the drug, and the latter complaint could be overcome in some instances by taking a full glass of milk with the medication.

DISCUSSION

Bronchial Asthma.—None of the antihistamine drugs used seemed to be as effective in the relief of bronchial asthma as the commonly used ephed-

rine compounds. There are a few isolated instances in which the subjective relief reported was quite marked. Objectively, this relief was not confirmed by a lessening of the physical signs of wheezing, dyspnea, et cetera. It is felt that these cases experienced relief for the most part from a psychotherapeutic aspect, rather than from an actual effect of the drug on the bronchial tree. It is also to be considered that the side effect of drowsiness, which the antihistamine drugs occasionally produce, might be an additional factor which could account for the relief of symptoms reported in these instances, and probably could be duplicated with any sedative. It is further to be borne in mind that hyposensitization therapy to the allergens suspected was continued throughout the investigation, and improvement was to be expected from this procedure even if no drug therapy was employed.

In those cases of asthma which were associated with pollinosis and were purely seasonal in character, a better response to the antihistamines was observed. However, even in these instances, the ephedrine compounds and Aminophyllin were at least as good and often more effective than the antihistamine drugs.

Hydryllin (Searle), which incorporates 100 mg. of Aminophyllin in each tablet seemed to give a higher degree of relief than the other antihistamine drugs, which produced about the same degree of relief when compared with each other. None of these drugs was as effective as the ephedrine compounds, such as Amesec (Lilly), Amodrine (Searle), et cetera, except in the case of asthma associated with pollinosis.

In *pollinosis,* however, it may be said that the antihistamine drugs studied play a valuable part in the physician's armamentarium. In those instances where hyposensitization therapy is not wholly successful, these drugs do more toward keeping the patient comfortable than anything else we have used to date. Particularly in those patients who are seen for the first time when the season is well in swing, the antihistamine drugs are truly a boon in a large majority of cases. They provide an inexpensive means of carrying the patient along through the symptomatic period until adequate effective hyposensitization therapy can make itself felt, i.e., the following year. These drugs also are of definite value in those cases in which sufficient resistance cannot be built up to weather heavy exposures to pollen asymptomatically. During these intervals, the judicious use of antihistamine drugs can change a moderately successful season to a practically asymptomatic one in many instances. In regard to the question as to which one of the drugs is the one of choice, a clear-cut opinion is hard to reach. The patients seem to vary in their responses to the drugs, with as many obtaining relief from one drug as from another. When the degrees of relief are totaled, Pyribenzamine and Histadyl seem to be slightly more effective than Benadryl, and Hydryllin and Compound 1695 are of slightly less benefit. It is to be granted that in the pollen cases, the pollen counts might have varied to such a degree as to cause false

evaluation of the efficacy of the drugs employed. For example, a drug reported as being of great value during the pollen season, might well have been employed during an interval when the pollen count was low, and the patient ordinarily would have felt better anyway. All, however, are of clear-cut benefit in pollinoses, and the efficiency of each is so close to the other that no conclusion can be drawn definitely.

In *allergic rhinitis,* the same comments seem to hold. There were fewer studies made with Histadyl than with the other drugs, and the writer gains the impression that possibly this drug seems a little more effective than do the others employed, although, numerically, the drug did not total as many points as did the others. Pyribenzamine seemed a trifle more effective than Benadryl, Hydryllin, or Compound 1695, but again the difference was so small as to be questionable.

Concerning *urticaria,* it must be remembered that some of these cases may have cleared spontaneously as time progressed. However, the antihistamine drugs exerted a definite beneficial effect. In no case observed were these drugs without some degree of value, and in a majority of cases, the relief afforded was dramatic and gratifying, both subjectively and objectively. In a few cases, the urticarial manifestation appeared chronic and the drugs were administered over prolonged periods of time. There seemed to be a tendency for the effect to be lessened as time went on, and the dosage or frequency of administration had to be increased. All of the antihistamine substances seemed of equal value with the possible exception of Compound 1695, which did not seem quite as effective as the others. It would seem that the selection of the drug to employ rests on individual tolerance and response.

In *gastrointestinal allergies,* the studies are far too few and incomplete for comment. The answer to this problem undoubtedly lies in the elimination of the offending allergen, and the part played by the antihistamine drugs is of far less importance. One case of colitis of mild degree in an emotionally unstable woman seemed to show temporary beneficial effect from the administration of Histadyl.

In *migraine,* too few cases were observed to evaluate. The use of ergotamine and its derivatives, plus avoidance of the offending foods, seems to give better results than the antihistamine drugs. No one antihistamine preparation was more effective than the rest.

Allergic Dermatosis.—Insufficient cases presenting involvement of the skin were observed in this study to be of significance. It was the writer's opinion that the antihistamine drugs play a minor therapeutic role here. They seem to have some effect in allaying the pruritus and, in this way, might allow for the healing process to take place without the hindering effect of the trauma induced by scratching. No particular drug appeared to excel in a significant degree. Perhaps Histadyl was a little more effective than the others, and Compound 1695 the least beneficial. Pyribenza-

mine, Benadryl and Hydryllin were about equal in their effect. Here again, the standard allergic and dermatological form of therapy are of more importance than these drugs.

Emotional Status.—It is interesting to observe the correlation concerning the presence of emotional instability and allergic complaints. It is granted that if one looks for evidences of emotional conflict, they will be found in any group of cases in any field. But in this particular group studied, the writer was impressed with the fact that twenty-five individuals, or nearly 30 per cent, had this complication in moderate or marked degree. In these individuals, beneficial responses were reported much more frequently than in the others, and the degree of benefit was greater. The writer gained the impression that this response correlated with the mood of the subject and was primarily subjective rather than confirmable by objective findings. Again the sedative effect of the antihistamine drugs must have been an important factor. It must also be granted that the mere fact that these cases were given the opportunity to express their difficulties vocally to a sympathetic listener must certainly have played a part in the amelioration of symptoms. One is forced to draw the conclusion that statistics concerning evaluation of benefits of drugs in this group are probably unreliable to a greater degree than in stable individuals. Possibly, the greater degree of benefit reported in other studies of this nature rested on including a large percentage of people so afflicted. If this be the case, the personality of the physician will affect the response no end, and the beneficial effect of the drug will not reflect itself to the same degree in the hands of another physician. Along this same line, it might well be emphasized that here is a potential means of treatment which should not be neglected. Mere sympathetic listening to these patients, and possibly offering helpful suggestions directed toward lessening the tension and conflict in their daily lives, will of itself bear gratifying results.

On the whole, the best response to the antihistamine drugs was seen in pollinosis, vasomotor rhinitis and urticaria. There was considerably less relief in the cases of bronchial asthma, especially of the perennial type, migraine and allergic dermatosis.

There seemed to be a correlation between the presence of emotional factors and the reported marked improvement from the antihistamine drugs, in a significant number of cases. This was emphasized further by the observation that this same group of patients obtained relief in several instances from the placebo which was employed. It was further observed that the objective, measurable improvement very frequently did not parallel reported subjective improvement, and this further emphasized the psychic factor as an important one. It is also to be borne in mind that definite continued improvement was to be expected in a goodly number of these cases from the hyposensitization therapy which they were receiving, even though no drugs were administered.

And so, considering the many different factors which play a part, i.e., emotional status, pollen counts, hyposensitization therapy, improvement based solely on subjective reporting, et cetera, only the vaguest generalities can be drawn.

This much we feel can safely be deduced. First, the antihistamine drugs are not dangerous to use in most instances. Second, they have a temporary beneficial effect in certain allergic conditions. This beneficial effect is most definite in pollinosis, urticaria and allergic rhinitis. Third, the beneficial effect obtained in perennial asthma, migraine and allergic dermatosis is of no better degree than that obtained with many other drugs, and often not as good. Fourth, these drugs, in their present form, will not replace the standard procedures for treating allergic disease, i.e., elimination of offending allergens, hyposensitization therapy, attempts at minimizing the emotional factors, maintaining the patient's general health in its best possible degree, et cetera. At best, the antihistamine drugs are only an adjuvant to these cardinal objectives.

Specifically, no one antihistamine drug was notably superior to the others. The writer feels that the side effects are slightly lessened when Histadyl is employed, as compared to Benadryl and Pyribenzamine. Hydryllin appears to stand somewhere between Histadyl and the others in this regard. In perennial asthma, better results are obtained with compounds containing ephedrine and Aminophyllin than with the antihistamines employed in the study.

SUMMARY

A group of patients manifesting a variety of commonly encountered allergic manifestations was observed, and the effects of a few antihistamine preparations were noted. An attempt was made to evaluate these effects in an endeavor to determine if one preparation was superior to the rest in the alleviations of these complaints. The responses to the drugs were variable and inconsistent in many of the conditions studied. Many factors other than the drug proper played a part in the patient's complaints. Not unimportant among these were the emotional state of the subject, the effect of seasons, the hyposensitization treatment being given, the self-limitation of some of the conditions, et cetera.

CONCLUSIONS

The antihistamine drugs are of palliative value in pollinosis, urticaria, and allergic rhinitis. They exert a lesser and almost insignificant effect in most cases of bronchial asthma, other than the asthma occurring during attacks of pollinosis. Their effect on gastro-intestinal allergic phenomena is undetermined due to the fact that insufficient material was observed.

Of the five antihistamine preparations studied, there is not much choice as to which is better than the others. All appeared to have about the

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SENSITIVITY TO A SPECIFIC HUMAN DANDER

LESTER L. BARTLETT, M.D., F.A.C.A.
Pittsburgh, Pennsylvania

THE fact that human dander may be a cause of allergic conditions has been known for many years.

Van Leeuwen and Van Niekerk[3] described a substance prepared by extracting human hair and dander which gave positive intradermal skin tests in allergic individuals and negative tests in nonallergic persons.

Cooke and Hampton[1] observed that the majority of patients suffering from allergic dermatitis were reactive to human dander extract, but that "other allergics" and normal persons never reacted in this manner. The authors were inclined, therefore, to believe that there is a relationship between allergic dermatitis and human dander sensitivity.

In a series of fifty cases tested with human dander, with epidermis from the sole of the foot and from the arms and legs of a newborn infant, as well as with vernix caseosa, with scrapings from the lesions of seborrheic dermatitis, with scales from exfoliative dermatitis, and with human serum, Simon[2] found that in five patients the reactions to human dander and seborrheic dermatitis were positive. All of these five positive cases had atopic dermatitis. Passive transfer reactions to human dander were obtained with the sera of each of these patients. The controls in normal skin sites were negative.

Simon then investigated the source and nature of the allergen, which led to the belief that the allergen is not a constituent present in stratified squamous epidermis in general, for patients who give skin reactions to human scalp dander and human scalp hair do not react to epidermis from the general body surface of an adult and a newborn infant, or to hair, sebaceous material, and the inner lining of a dermoid cyst, or to scales from psoriasis and exfoliative dermatitis.

CASE REPORT

The patient, a twenty-eight-year-old white woman, was first seen September 8, 1942, at which time she had an allergic dermatitis involving the face, neck, anterior surface of the upper chest, hands, forearms and cubital spaces. At the age of four months she developed eczema of the face and of the cubital and popliteal spaces. Although she had no treatment, the eczema disappeared spontaneously at the age of fifteen years. When the patient was eighteen years of age, she developed the fall type of hay fever, which recurred each year after that time. No treatment was ever given. In November, 1940, she became engaged, and about that time she noticed an occasional eczematous area on her face, which would persist for a few days. She was married the following year, and within a few days, several eczematous areas appeared on her face. These lesions were very itchy and became larger and more scaly. Within a short time she developed areas on her hands and forearms, and when first seen she had involvement of her entire face, neck, upper chest, hands, forearms and cubital spaces.

She was skin-tested routinely with the common foods and inhalants. There were

marked positive reactions to house dust, feathers, goat dander, cornmeal, cabbage and ragweed. There were only moderate reactions to cotton seed, silk, barley, oatmeal, pea, onion, string bean and lemon. Patch tests were done with her cosmetics and with her husband's shaving cream and brilliantine. Of these she had positive reactions to brilliantine, cologne and nail polish. *She showed no reaction to stock human dander.* All cosmetics were removed from her environment, and she was given a diet in accordance with the results of the skin tests. Desensitization was initiated with stock dust extract to which were added extracts of feathers, cotton seed and goat dander. Coseasonal treatment with ragweed pollen extract was instituted at the same time. Following this routine there was very slight improvement of her skin, but the hay fever was less severe than in previous years.

On January 20, 1943, her husband was inducted into the army. About March 1, 1943, her skin was entirely clear, and she had no return of the lesions until August 15, 1943. This occurred while she was visiting her husband who was stationed in an army camp. The skin lesions appeared first on her face and then spread to her neck, upper chest, hands and forearms. After one month she returned home, and within one week after her return home the dermatitis had disappeared again.

The patient did not consult us again until February 20, 1946. At that time she gave the following interval history. She visited her husband again in February, 1944, and the dermatitis recurred within a few days and was present until about one week following her return home. Her husband was sent overseas and remained there for sixteen months. During this period there was no recurrence of the dermatitis. Her husband returned home, and within one week following his return, the dermatitis had recurred on all the areas that had been involved previously.

Two weeks after her husband's discharge from the army, dander was taken from his scalp and body, and patch scratch tests were done with each. A positive reaction was found from the scalp dander, in contrast to the negative reaction that was observed with the stock extract. The body dander showed no reaction.

Scalp dander and scalp hair were collected, and an extract was prepared. Intradermal tests were done with this autogenous scalp dander extract and again with the stock human scalp dander extract. The test with the autogenous scalp dander was positive, while that with the stock human scalp dander was negative. Passive transfer reaction was obtained with the autogenous scalp dander extract.

Treatment was started with the autogenous extract April 25, 1946, and by September 1, 1946, the lesions on her face, neck and chest had cleared, but some of the lesions on her hands were still present. Treatment was continued, and all the lesions had disappeared by June 15, 1947. Treatment is still being continued, but the interval between treatments has been lengthened. The foods which were restricted have been returned to her diet. At the time of this report there has been no return of the lesions.

Twenty control patients were tested with this specific human scalp dander. Ten of these patients had previously shown positive reactions to stock human dander extract, and ten had been negative. Of these, nine of the previous positive patients showed positive reactions to the specific human dander, and one was negative. The other ten controls were negative.

The author has previously noted the fact that no instance of sensitivity to a specific human scalp dander has been observed and reported—that is to say, a patient sensitive to scalp dander from one individual and not showing positive reaction to various stock human dander extracts.

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SPONTANEOUS RIB FRACTURE IN BRONCHIAL ASTHMA

MAXWELL L. GELFAND, M.D., F.A.C.A.

New York, New York

MANY authors have recorded spontaneous fracture of one or more ribs as a result of violent coughing. Although in most instances, these were associated with pulmonary tuberculosis, many other causes, such as severe bronchitis, pneumonia, atypical pneumonia, pertussis and foreign body, have been mentioned. Bronchial asthma, a condition in which cough is a most distressing symptom, has rarely been indicted.

Halliwell,[2] in 1929, reported a case of a physician who had influenza with an asthmatic type of bronchitis and, in an episode of severe coughing, fractured his sixth, seventh, eighth and ninth ribs. Oechsli,[3] in 1936, reported twelve cases of fractured ribs, of which eleven were associated with far advanced tuberculosis and the twelfth was a patient with bronchial asthma and bronchitis. Swineford and McKennon,[6] in 1945, reported a case of multiple fracture of the ribs in a case of bronchosinusitis.

The following case is reported because of the infrequent occurrence of spontaneous rib fracture in bronchial asthma, and to call attention to this possibility in asthmatic patients who complain of severe chest pain.

CASE REPORT

J. La S., a white male, sixty-eight years of age, was admitted to Bellevue Hospital, Fourth Medical Division, New York University, on February 14, 1947, complaining of severe cough, dyspnea and pain in the right chest. His past history disclosed that he had been suffering from bronchial asthma for the past twelve years and from pernicious anemia for seven years. For the latter disease he had been adequately treated with liver extract until ten months previously. There was no history of any recent chest injury.

His physical examination revealed that he was considerably dyspneic, orthopneic and somewhat cyanotic, but well developed and well nourished. His pupils were equal and regular, and reacted to light and accommodation. His fundi were normal. His neck was supple, and his trachea was in the mid-line. His chest revealed an increase of his anteroposterior diameter with hyperresonance throughout. On percussion there was tenderness in the right side of the chest, at the level of the ninth rib in the posterior axillary line. Tactile and vocal fremitus were decreased. There were diminished breath sounds, and many rhonchi, wheezes and subcrepitant râles were heard in both lung fields. His heart revealed distant heart sounds with normal rhythm. No murmurs were detectable. His aortic second sound was somewhat louder than his pulmonic second sound. His blood pressure was 140/90. His abdomen was soft, with the liver extending two finger breadths below the costal margin. There were no other palpable viscera. His extremities were not edematous, and there were no signs of inflammation. His reflexes were entirely physiological.

His blood count revealed a red cell count of 4,370,000 with a hemoglobin of 13.2 gm. His white cell count was 10,200, with 67 per cent polymorphonuclear cells, 2 per cent transitional cells, 25 per cent lymphocytes, 6 per cent monocytes, and 5 per cent eosinophiles. His total blood proteins were 7.6 gm. per cent, of which the albumin was 4.1 gm. per cent and the globulin was 3.5 gm. per cent. His blood acid

phosphatase was 1.8 units per 100 c.c., and his alkaline phosphatase was 3.8 units per 100 c.c. His blood calcium determination was 9.5 mg. per cent, and his blood inorganic phospherous was 2.5 mg. per cent. His blood nonprotein nitrogen was 30 mg. per cent. The Mazzini test for syphilis was negative. His urine examination on February 14, 1947, disclosed a specific gravity of 1.025 with no albumin or sugar present. On microscopic study, seven white blood cells and few epithelial cells were detected. The Bence Jones test was negative. The venous pressure was 85 mm. of water, and the circulation time was fourteen seconds with decholin and eight seconds with ether.

X-rays of the chest taken on February 14, 1947, disclosed a fracture of the eighth, ninth and tenth ribs on the right side. Intravenous pyelography revealed normal kidney outline. A repeat chest film several months later showed callous formation over the eighth, ninth and tenth ribs on the right side.

He ran a low grade fever ranging from 100° to 101° C. for the first four days of his hospital stay, and after therapy his temperature returned to a normal level. He was treated with Vaponefrin by aerosol inhalation, followed by penicillin aerosol, 40,000 units every four hours. In addition he received aminophylline by rectal catheter instillation. His chest was strapped, and 100 mg. of Demerol intramuscularly was given for his pain. He continued to improve on this regime, and on his twentieth hospital day he was discharged to the allergy clinic for follow up.

COMMENT

The absence of a history of trauma, the failure to demonstrate any involvement of the osseous system, bone decalcification or metastases, and the marked clinical and x-ray improvement favor a diagnosis of spontaneous rib fracture as a result of spasmodic coughing during an attack of bronchial asthma. Several explanations have been offered as the probable mechanism involved in spontaneous fracture of the ribs associated with coughing. It has been advanced by Sabbione,[4] who studied rib fractures in tuberculosis, that the cause was decalcification of bones secondary to tuberculosis. Tunis[7] and Seilin[5] propounded the idea that contraction of the diaphragm may be a cause of the fracture. This, however, is difficult to accept because the attachments of the diaphragm do not correspond to the usual line of fracture. Bond[1] feels that fracture of the ribs as a result of cough is a fatigue fracture, similar to March fracture found in new recruits and those performing unusual physical exercise. The most logical explanation based on anatomic and physiologic principles was clearly pointed out by Oechsli,[3] who felt that the opposing action of two sets of muscles is necessary in the production of this type of fracture. The contraction of the serratus anterior, which exerts a pull laterally and cephalad, as opposed to the simultaneous pull of the external abdominal oblique medially and caudad, is most likely the determining factor. This may be the reason for the rare occurrence of spontaneous rib fracture in bronchial asthma. Although coughing occurs frequently in the latter disease, the added factor of opposing action of muscles does not always exist.

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STUDIES OF DRUG SENSITIVITY

O. C. HANSEN-PRUSS, M.D., F.A.C.A.
Durham, North Carolina

THE problem of drug allergy is a complex one, and has assumed increasing importance since the introduction of the sulfonamides[8,9] and, more recently, the antibiotics. Sherman[10] reviewed the subject a few months ago, and he pointed out that the available methods for the demonstration of the sensitivity to drugs were, as yet, quite unsatisfactory. This was particularly true of the intracutaneous tests with crystalloid drugs. Furthermore, he pointed out that so far it had been impossible to demonstrate circulating antibodies in patients suspected of a sensitivity to drugs. Whittemore and de Gara,[11] however, recently reported one patient in whom it was possible to prove the existence of circulating antibodies to sulfadiazine, by successful passive transfer tests. The supposedly allergic reactions to penicillin have been discussed fully in an article by Farrington, Olansky, and Riley,[2] which also contains an excellent bibliography of the subject. These authors felt that the reactions to penicillin are probably on an antigen-antibody basis; they also remarked that cutaneous tests are of limited value and often inconclusive.

In a recent article we reviewed the available methods for the objective demonstration of suspected drug sensitivity.[4] It was pointed out that the pessimism surrounding this subject was perhaps unwarranted, and largely the result of the failure of any one method of testing to prove valid in all of the many types of hypersensitivity produced by the myriad drugs now in daily use.

About two years ago, we investigated the effect of a group of analgesic and antipyretic drugs on the peripheral blood and on the bone marrow of a group of normal medical students.[5] Reports of sensitivity to drugs such as aspirin,[1,3] and other similar compounds, abound in the medical literature. We have next attempted to study a number of patients in whom a sensitivity to one of a group of analgesic and antipyretic compounds was suspected.

MATERIAL

During the past two years we studied a group of twenty-six patients suspected of being allergic to drugs. Only those patients were considered who were thought to be hypersensitive to one of the analgesic or antipyretic drugs. The drugs and the corresponding number of patients were as shown in the accompanying table.

Of this group, fifteen patients were subjected to complete investiga-

From the Department of Medicine, Duke University School of Medicine, Durham, North Carolina.

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tion, and eleven were partially studied. Women comprised the majority of this group, namely, twenty-three; the age period varied from twenty to fifty-three years. The subjects were chosen because of: (1) a fairly convincing history of hypersensitivity to one of the above-mentioned drugs, (2) a personal history of one of the common allergic disorders, (3) a positive or presumptive family history of the common allergic disorders, and (4) a combination of any of the above requirements.

Drugs	*No. of Patients*
Aspirin	17
Sd. Salicylate	3
Acetophenetidin	1
Acetanilid	2
Aminopyrine	3
Total	26

Fifteen of these patients (fourteen women and one man) gave an unequivocal history of urticaria; ten, of urticaria and angioneurotic edema (two men and eight women), and one woman had experienced the above and also definite bronchospasm after the ingestion of the drug. Very careful questioning of these patients, and particularly of those who gave a history of other allergies, showed that it was hazardous to assume that the allergic reaction to a drug was uniformly urticaria. One of the women in this group, for instance, also presented a hematological problem, namely, leukopenia. It is quite probable that this is not an important point, since it has been emphasized frequently that the allergic reaction to drugs is quite variable, often polymorphous and complex. The allergic background of this group of patients and their reaction type is shown as follows:

Positive F.H.	*Positive P.H.*	*Males*	*Females*	*Type Reaction*
5	3	0	13	Urticaria
3*	2	2	7	" ang. edema
0	0	1	2	" asthma
0	0	0	1	" leukopenia
8	5	3	23	

*No males.

It is quite obvious that this group of patients is too small to justify any conclusions regarding the role of a predisposition to allergic disorders in determining the occurrence of sensitivity to drugs. It would, perhaps, also be hazardous to emphasize the great preponderance of female patients in this group of drug-sensitive individuals. On the other hand, one might speculate that this is not only the result of happenstance, or of the greater concern of women with sometimes minor complaints, but perhaps a natural sex-linked phenomenon.[6] Further studies are certainly indicated to determine if women are more prone to develop a drug sensitivity, than are men.

METHODS

(1) Every selected individual was, of course, subjected to a thorough clinical study (anamestic and physical survey) which included complete and repeated examinations of the peripheral blood and, in some instances, bone marrow studies. (2) Intracutaneous skin tests to the common allergens, such as pollens and other inhalants, contact, food allergens, and to a series of fungi extracts were done on most patients of this group. (3) Intracutaneous tests to (a) solutions of the suspected drug, (b) to serum obtained from patients supposedly saturated with the suspected drug, were carried out on fifteen patients. (4) Mucous membrane contact tests with the drugs were done on six patients. (5) Passive transfer tests were included in the study of five patients. (6) Tests with "blister fluid" were possible in two patients. (7) In two patients the suspected drug was readministered.

The *controls* were a group of individuals who gave no familial or personal history of allergy, and who failed to give positive reactions to the intracutaneous injection of the common test allergens. Since these studies were quite fluid in scope, and since not all the patients were subjected to the same tests, controls were only used when necessary to evaluate the significance of an observation.

The *blood sera* which were used for testing were divided into two groups: (A) sera obtained from nonallergic and non-drug-sensitive individuals; (B) sera drawn from patients with a suspected drug allergy. The sera of group A were used for intracutaneous tests on controls, as well as on supposedly drug-sensitive individuals. An initial specimen was obtained from the individual before the administration of the drug; this was used as a "control." Another sample was then drawn from the same subject after he or she had received the drug in question orally for a period of two or three weeks. The sera of group B were used for intracutaneous tests on normal people, as well as on supposedly drug-sensitive patients. The drug-sensitive subjects were not only tested with sera obtained from other individuals with an allergy to the same drug, but also with sera from patients apparently allergic to other drugs of the group, which is the subject of this study. The sera were drawn, whenever possible, after a fifteen-hour fasting period and were preserved with a small amount of an aqueous solution of methiolate. The test dilutions were 1:10, 1:100 and, whenever indicated, 1:1000. The test dose was 0.1 c.c., injected intradermally. The reactions were read at the following time intervals after injection: twenty minutes, twenty-four hours, and thirty-six hours. The positive wheal reactions were measured with a planimeter, and recorded in square centimeters.[7] The area of the accompanying erythema was also measured similarly and recorded.

A *blister fluid* was obtained from two patients, and this fluid was used for direct skin tests on one supposedly normal individual, and two drug-

sensitive patients. Unfortunately these patients did not suffer apparently from an allergy to which the donor patients were subject. The blister fluid was aspirated with a sterile tuberculin syringe, cultured on blood agar plates and then used for testing in a 1:10 dilution. No preservative was added since the fluid was small in amount and was used promptly after the culture was reported.

The technique of *bone marrow studies* has been described elsewhere.[5] It suffices to say that the results observed in this group of patients differed little from those previously reported in patients receiving these analgesic and sedative drugs.

RESULTS

It is impossible to tabulate the over-all picture of these various tests for drug allergy. The results of the investigations varied so greatly, not only from one group of patients to another, but also within a given patient group, as to make a statistical comparison hazardous. The observations must, therefore, be presented separately with illustrative examples.

Skin Tests.—These observations can be divided into two main groups: (1) the result of direct intracutaneous skin tests to drug solutions, and (2) the result of passive transfer tests.

The direct skin tests to solutions of these drugs were done in fifteen patients who were suspected to be allergic to one of these drugs. As has already been stated, the test solution contained the drug in a supposedly neutral vehicle. Of these fifteen patients tested, all but one gave a positive wheal reaction to the intradermal injection of 0.1 c.c. of the drug in a 1:10 dilution. One patient reacted with an area of erythema measuring 2 cm. after twenty minutes, following the injection of 0.1 c.c. of a 1:100 dilution of the drug test solution; no wheal reaction was observed. Delayed reactions (after twenty-four and forty-eight hours) in this group were so variable that they could not be interpreted satisfactorily. It soon became apparent that direct skin tests with drug solutions in suspected drug allergic individuals were unreliable, since a control group of evidently nonsensitive and non-drug-allergic subjects chosen at random gave analogous skin tests to these analgesic drugs. Tests were then done with sera obtained from nonallergic patients who had received the analgesic or sedative drug over a period of time which was considered adequate to "saturate" such a patient. It is true that saturation in such an instance is only an assumption, but the results obtained are interesting:

N. H., a white woman, aged forty-four years (H. No. B80566) had a history of recurrent urticaria over a period of ten years, not related to any factors which could be elicitated by a close study of the patient's history. She was primarily referred to this hospital because of a persistent leukopenia of about fourteen months' duration. This leukopenia could not be ascribed to any preceding infection or drug therapy, and the patient denied the use of aminopyrine. The patient stated, however,

that she had been in the habit of taking headache powders containing, presumably, acetanilide and also aspirin, not only for the relief of recurrent headaches but also for general surcease of nervousness. The physical examination showed as only abnormalities obesity and an impacted molar tooth. She had leukopenia without anemia or thrombopenia; the differential white blood cell formula showed an absolute decrease in myeloid cells; the bone marrow studies were essentially normal (no eosinophilia). The patient was skin tested to all of the common inhalant, contact and food allergens, and to a number of fungi extracts, and no positive reactions were observed. She was now skin tested to homologous sera from patients who had been given these analgesic drugs in supposedly adequate dosage. The results are given below:

	Dilution	*Time*	*Reaction*
Sod. Salicyl. Serum*	1:10	30 min.	3 sq. cm.
"	1:100	30 min.	½ sq. cm.
Acetanilide "	1:10	30 min.	1 sq. cm.
"	1:100	30 min.	0
Aminopyrine "	1:10	30 min.	1 sq. cm.
"	1:100	30 min.	0
Aspirin**	1:10	30 min.	2½ sq. cm.
"	1:100	30 min.	1 sq. cm.
Antipyrine	1:10	30 min.	2 sq. cm.
"	1:100	30 min.	0
Control Serum	1:10	30 min.	½ sq. cm.
"	1:100	30 min.	0

* 1:1000 Dilution—½ sq. cm.
** 1:1000 Dilution—Negative.

These observations were now checked against a control. The control patient was a thirty-year-old white woman with chronic myelogenous leukemia (aA 49589) who had been under observation for five years. Her familial and past personal histories were entirely negative for the common allergic disorders. The patient failed to give any positive skin reactions to the intracutaneous injection of the common test allergens. She was skin tested to the same sera mentioned above. She gave positive or doubtful reactions to all of the sera within thirty minutes after the intradermal injection of 0.1 c.c. of a 1:10 dilution of the respective serum. However, at no time did the positive reaction exceed 1.5 sq. cm. The patient was then given aminopyrine, 0.9 gm., three times a day for twenty-five days. At the end of this time she was retested to sera obtained from patients who had received one of these analgesic drugs for at least three weeks. The skin tests now were essentially as before the administration of aminopyrine. Incidentally, it should be noted that aminopyrine did not influence in any way this patient's white blood cell count, the differential white blood cell formula, nor the bone marrow pattern.

Similar studies were carried out on twenty other patients. As stated before, intracutaneous tests to solutions of the suspected drug were soon abandoned because they were inconclusive. This is an observation frequently reported in the literature. Skin tests in drug-sensitive individuals with sera obtained from patients who received one of these drugs over a period of at least three weeks were not quite as inconclusive. For simplicity, the positive tests were tabulated as 1 plus, 2 plus, 3 plus, 4 plus; these correspond to wheal reactions measuring 1 sq. cm., 2 sq. cm., 3 sq. cm., and 4 sq. cm., respectively, and all were read twenty minutes and twenty-four hours after the intracutaneous injection of the test sera. The results in twenty other patients with a suspected drug allergy were as in Table I.

These observations are analyzed later in the discussion. Controls for

most of these tests were sera obtained from a number of normal individuals who had not taken any of these analgesic drugs for a period of at least four weeks. The control tests were uniformly negative.

TABLE I

Drugs	No. Patients	Reactions to Sera Containing Suspected Drug				Reactions to Other Drug Sera			
		1:10		1:100		1:10		1:100	
		30′	24 hrs.	30′	24 hrs.	30′	24 hrs.	30′	24 hrs.
Aspirin	3	++	0	+	0	0	0	0	0
	2	+++	+	+	0	++	±	0	0
	6	+	0	0	0	+	0	0	0
Sodium Salicylate	1	+++	+	++	±	0	0	0	0
	2	++	±	+	0	++	+	+	0
Acetanilid	1	+++	+	++	+	0	0	0	0
	1	++	±	+	0	++	±	+	0
Aminopyrine	1	+++	++	++	+	0	0	0	0
	2	++	±	+	0	++	±	++	0
Acetophenetedin	1	++	0	+	0	++	0	0	0

Passive Transfer Tests.—The results of these investigations, attempted in five patients who gave a history of drug allergy, were rather discouraging. In only one instance was it possible to obtain a "positive" test:

R. G. (No. A41495), a white male, aged forty-seven years, gave a history of recurrent bouts of urticaria and angioneurotic edema; he stated that most of these bouts followed the ingestion of aspirin. The patient's family and past personal histories were negative for the common allergic disorders, as were intracutaneous skin tests to the usual test allergens. The physical examination was not remarkable, except for the urticaria noted on admission. No foci of infection were noted. The peripheral blood and bone marrow pictures were normal. Direct skin tests to an aqueous solution of aspirin were positive up to a 1:1000 dilution. The patient also gave a 2 sq. cm. reaction to the intradermal injection of a 1:1000 dilution, and a 1 sq. cm. reaction to a 1:100 dilution of a serum obtained from an individual who had received 0.9 gm. of aspirin a day for three weeks. He did not react to a 1:10 dilution of a "control" serum (obtained from the same individual) drawn before the administration of aspirin. A suitable (nonallergic) subject was injected intracutaneously with 0.1 c.c. of serum obtained from the aspirin-sensitive patient. The prepared sites were then injected, forty-eight hours later, with 0.1 c.c. of sterile "inert" solutions of the mentioned analgesic drugs in a 1:10, 1:100, and 1:1000 dilution. All of the tests with the five drugs in a 1:10 dilution were positive, ranging from 2.5 sq. cm. with aspirin, to 1 sq. cm. with aminopyrine; the 1:100 aspirin solution gave a 2 sq. cm. reaction, whereas the reactions to the other solutions were doubtfully positive, and a 0.5 sq. cm. reaction was obtained with 0.1 c.c. of the 1:1000 solution of aspirin, whereas it was negative to the injection of solutions of the other drugs in a similar concentration.

In the other four patients the results of the passive transfer tests were inconclusive. Three were suspected of aspirin sensitivity, and one patient was considered to be allergic to sodium salicylate or to antipyrine. The

first three patients gave 1 to 2 sq. cm. reactions to the intradermal injection of 0.1 c.c. of a 1:10 dilution of the aspirin solution; one gave a 0.5 sq. cm. reaction to the 1:100 dilution, and none reacted to the 1:1000 dilution of this drug. Two of the three aspirin-allergic patients also gave comparable positive reactions to 1:10 and 1:100 dilutions of at least two of the other analgesic drugs (particularly sodium salicylate and antipyrine), and the other patient gave a stronger reaction to sodium salicylate and to antipyrine than to aspirin. As a matter of fact, the reaction in this patient was 1 sq. cm. to a 1:1000 solution of sodium salicylate, and 0.5 sq. cm. reaction to a similar solution of antipyrine and negative to a 1:1000 dilution of aspirin.

Readministration of the Drug.—This method of testing for drug sensitivity has been used extensively in this country and abroad, particularly when a sensitivity to one of the sulfa drugs was suspected. It was tried in two patients of this group.

One patient was the individual with urticaria and leukopenia, reported before. She had an average white cell count of about 2,000 per cu. mm., during the four weeks of her hospital stay. The suspected drug, aspirin, was administered in a single dose of 0.3 gm. There was no change in the white blood cell count of the peripheral blood, nor in the bone marrow pattern; furthermore, it did not provoke urticaria or angioneurotic edema. On the next day (peripheral blood picture unchanged) the patient was given 0.9 gm. of aspirin in a single dose; the results were again negative, although the patient complained of some itching of the skin (no visible eruption) four hours after the drug was administered.

The other patient was a young nurse, aged twenty-two years, who had been observed previously complaining of urticaria and generalized weakness. It was found that the latter coincided with a peripheral white cell count of 3,000 or less. She had taken aminopyrine off and on for relief of headaches. Examination failed to reveal any familial or personal history of a predisposition to allergic disorders, and skin tests to the common allergens were again negative. She gave a strong positive reaction of the immediate type, and a questionable positive reaction of the delayed type, to the intradermal injection of aminopyrine sera in a 1:100 dilution. Her serum was used for passive transfer tests with inconclusive, and certainly nonspecific, results (see above). The patient was observed in the hospital for some time, and when her white blood cell count had been checked as being normal repeatedly, she was given 0.1 gm. of aminopyrine by mouth. This produced no change in the peripheral white blood cell count and no cutaneous reaction. She was then given 0.3 gm. of aminopyrine; the peripheral white blood cell count, which was checked each fifteen minutes, dropped to 1,500 per cu. mm. in thirty minutes and remained below normal for nine hours. During this time she had a slight elevation in temperature (maximum 38.2° C.), some injection of the bulbar conjunctivae, but no skin eruption. There was no appreciable change in the bone marrow picture, and at no time did she show an eosinophilia in the peripheral blood or in the bone marrow. Furthermore, she did not react more strongly to intradermal tests with aminopyrine solutions, or with solutions of any of the other analgesic drugs studied, nor was her serum more effective in producing positive transfer tests when drawn at the height of her allergic reaction, nor when obtained twenty-four hours later, after her symptoms had subsided and her temperature had become normal.

DISCUSSION

First of all, it should be re-emphasized that intracutaneous tests with a solution of the analgesic drugs used in this study are inconclusive. This conforms with the observations of many investigators who used not only such drugs but solutions of a number of other drugs, such as various sulfa preparations and penicillin. However, in certain instances, a very strong positive immediate reaction to a drug solution, particularly in a solution of 1:100 or 1:1000, may indicate not only a probable skin sensitivity to such a drug but perhaps also a systemic sensitivity, as suggested by the reported observations.

The skin tests with sera obtained from individuals who were given one of these drugs over a period of three weeks were, broadly speaking, nonspecific. In the majority of instances positive cross reactions were obtained, i.e., a patient with a suspected allergy to aspirin gave a positive reaction, not only to aspirin-serum, but also to aminopyrine, sodium salicylate, acetanilid, or antipyrine. As far as could be determined, a positive reaction to one of these sera did not necessarily invite a positive test to a specific of one of the other drugs of this group. Two observations seem to be quite valuable:

1. A group relationship apparently exists, so that patients who are suspected to be aspirin-allergic usually will also give a positive reaction to sera from patients who received sodium salicylate, 0.3 gm. a day for three weeks.

2. As a rule, patients suspected of being sensitive to one of this group of analgesic drugs gave much stronger reaction to the intradermal injection of a serum which apparently contained the drug, than to other sera. The most convincing results, as far as skin tests are concerned, were obtained in patients who were presumably aspirin-sensitive, and with aspirin sera. It seems that aspirin is a strong allergenic substance. This observation is substantiated by the recorded results of the passive transfer tests, since in only one of five patients was it possible to demonstrate unequivocally the passive transfer of a sensitivity to one of these drugs, and this drug was aspirin.

Since only two patients were tested with blister fluid, no conclusions can be drawn, but it seems obvious that this method of testing for drug sensitivity has many limitations, particularly the fact that it is very difficult, in most cases, to obtain the blister type of reaction.

The test which is founded on the readministration of a specific drug seems most reliable, but is subjected to obvious limitations, especially those which might endanger the life of the patient.

CONCLUSIONS

1. There is no single testing method to prove or disprove the existence of drug allergy in a given patient, or in a group of patients, when one of the analgesic or sedative drugs is involved.

2. Intracutaneous skin tests to solutions of such drugs are unreliable.

3. Intradermal skin tests with sera obtained from nonallergic individuals who received one of these drugs orally in a dosage of at least 0.3 gm. a day for three weeks were nonspecific.

4. As a rule, patients sensitive to one of these drugs will react more strongly to the intradermal injection of the serum containing the particular drug than to sera from individuals who received one of the other drugs of this group.

5. Patients suspected of being sensitive to aspirin usually reacted strongly not only to aspirin serum, but also to sodium salicylate serum; the reverse was also true.

6. There were no significant changes in the peripheral blood and bone marrow pictures in this group of patients.

7. In only one of five patients was it possible to demonstrate a passive transfer of drug sensitivity, and this was with the serum of an aspirin-sensitive individual.

8. The results observed in this group suggest that aspirin is perhaps the strongest allergenic drug of this group of analgesics and sedatives.

9. Each patient suspected to be allergic to a drug must be subjected to not one but to a series of tests before such a suspected sensitivity is discarded or accepted.

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ORAL POLLEN ABSORPTION

Demonstrated by Controlled Passive Transfer Tests

THEODORE M. FEINBLATT, M.D., and ROBERT LOVE, M.D.
Brooklyn, New York

THE desirability of a rational oral therapy for allergic rhinitis is obvious. Application of controlled passive transfer tests has demonstrated the theoretical basis for oral antigen treatment. The following observations have proven the feasibility of this type of treatment.

Positive reactions of remote passive transfer sites have shown that the oral antigen is effectively absorbed from the gastrointestinal tract.

Quantitative comparison with the effect of a parenteral dose of commercially produced antigen has shown that practical results may be economically achieved with oral antigen therapy.

The absorption of oral pollen preparations from the gastrointestinal tract[3,5] has been demonstrated. The treatment of allergic rhinitis due to pollens[1,2,6,7] has also been demonstrated. The use of controlled passive transfer reactions showing quantitative comparisons with parenteral injections has not been reported in the literature.

MATERIALS USED

Oral Antigen (Processed Mixed Pollens).—Each capsule contained 12 mg. Ambrosia trifida, 12 mg. Ambrosia elatior (giant, dwarf ragweed) and 6 mg. of mixed orchard, lawn grass and common pollens.*

This mixture was processed by hydrolysis and used in the form of capsules. Each capsule contained a total of 30 mg. of processed pollens together with a filler of rosebud-flour.

Commercially Produced Antigen (Parenteral).—Mixed grasses and ragweed extract, combined (Lederle), was used throughout. This was diluted with diluent (Lederle) so that each 0.5 c.c. contained 1,000 pollen units** (1,000 micrograms of pollen).

Passive Transfer Serum.—This consisted of the natural blood serum of an individual who was proven sensitive to ragweed or to summer grasses. No preservative was added. All the sera were tested for sterility and

Dr. Feinblatt is a Fellow in the Department of Physiology, Long Island College of Medicine, and Dr. Love is in the Department of Medicine, Kings County Division, Kings County Hospital, Brooklyn, New York.

*Orchard grass (Dactylis glomerata) 100 gm.
Timothy (Phleum pratense) 100 gm.
Goldenrod (Solidago canadensis) 10 gm.
Pin Oak (Quercus palustris) 20 gm.
Rye (Secale cereale) 10 gm.
Jerusalem Oak (Chenopodium botrys) 1 gm.
Spiny Amaranth (Amaranthus spinosus) 1 gm.
Annual Wormwood (Artemisia) 1 gm.
Aster (cultivated) 1 gm.
Rye Grass, Perennial (Lolium perenne) 1 gm.
Tree-of-Heaven (Ailanthus glandulosa) 1 gm.

**It has been noted that various brands of parenteral antigens, each labeled 1,000 pollen units, give different degrees of erythema in the same subject under controlled conditions. This suggests a difference in antigen response not reconciled by the usual method of assay.

Wassermann reaction. Previous observations had demonstrated the thermolabile nature of these sera. For this reason sera were kept refrigerated. They were used within two weeks.

TABLE I. CLINICAL MATERIAL

Case No.	Age (Years)	Height (Inches)	Weight (Pounds)	Sex
1	62	66	120	F
2	23	70½	165	M
3	55	56½	98	F
4	50	63	125	F
5	63	60	102	F
6	21	63	135	F
7	46	61	120	F
8	28	66	154	M
9	34	60	140	M
10	41	62	100	F
11	55	60	100	F
12	32	67	133	M
13	58	60	130	F
14	40	60½	175	F
15	55	65½	180	F
16	49	60	135	F
17	44	64	130	F
18	22	61½	100	F
19	45	62	120	F
20	34	70	120	M
21	57	62	122	F
22	25	63	140	F
23	48	59	105	F
24	47	64	120	F
25	26	65	135	M
26	57	66	145	M
27	61	62	142	F
28	54	64	130	F
29	57	64	100	M
30	17	66	142	F
31	43	66	125	F
32	35	67	100	M
33	72	64	150	F
34	57	64	110	F
35	33	65	127	F
36	32	62	96	F
37	45	70	220	F
38	48	64	148	F
39	45	61	120	F
40	28	73	168	M
41	22	61	190	F
42	63	62	120	F
43	24	62	151	F
44	44	67	184	F
45	22	64	145	F
46	34	69	170	M
47	29	61	110	F
48	28	70	165	M
49	24	67	130	F
50	32	66	128	F
51	29	61	110	F
52	30	62	110	F
Average:	40.9	63.9	133.5	40-F 12-M

CLINICAL MATERIAL

Passive Transfer Donors.—These passive transfer donors were selected because they had a clinical history of sensitivity to ragweed or to grasses. Skin tests verified the specific nature of the sensitivity.

The age, height, weight and sex of these individuals are detailed in Table I, according to Case number.

Passive Transfer Subjects.—Individuals who were not sensitive to ragweeds or lawn grasses were selected as passive transfer subjects. Individuals with no allergic background were preferred.

Cases 1 through 52 show an average age of 40.9 years, height 63.9 inches,

and weight 133.5 pounds. There were forty females and twelve males in the group. These findings are detailed in Table I.

TABLE II. RESULTS

Case No.	Transfer reaction	Oral Antigen	Parenteral Antigen	Greatest Reaction (Hours) Oral	Parenteral
1	positive	positive	positive	1.75	2.25
2	positive	negative	positive	2.25	1.75
3	positive	positive	negative	1.75	*
4	positive	positive	negative	2.25	3.75
5	positive	positive	positive	1.50	1.50
6	positive	positive	negative	1.50	*
7	positive	negative	positive	*	1.75
8	positive	positive	negative	5.50	3.50
9	positive	positive	negative	4.00	3.75
10	positive	positive	positive	2.75	2.50
11	positive	negative	positive	*	.75
12	positive	negative	positive	*	2.00
13	positive	positive	negative	3.75	.25
14	positive	negative	positive	*	2.75
15	positive	positive	negative	2.00	1.00
16	positive	positive	positive	2.00	2.00
17	positive	positive	positive	1.00	1.75
18	positive	positive	positive	2.00	5.50
19	positive	positive	positive	2.00	1.25
20	positive	positive	positive	2.00	2.00
21	positive	positive	positive	1.00	2.50
22	positive	positive	positive	6.00	2.75
23	positive	positive	positive	3.00	2.50
24	positive	positive	positive	2.75	1.75
25	positive	positive	positive	4.00	3.00
26	negative	*	*	*	*
27	negative	*	*	*	*
28	negative	*	*	*	*
29	negative	*	*	*	*
30	negative	*	*	*	*
31	negative	*	*	*	*
32	negative	*	*	*	*
33	negative	*	*	*	*
34	negative	*	*	*	*
35	negative	*	*	*	*
36	negative	*	*	*	*
37	negative	*	*	*	*
38	negative	*	*	*	*
39	negative	*	*	*	*
40	negative	*	*	*	*
41	negative	*	*	*	*
42	negative	*	*	*	*
43	negative	*	*	*	*
44	negative	*	*	*	*
45	negative	*	*	*	*
46	negative	*	*	*	*
47	negative	*	*	*	*
48	negative	*	*	*	*
49	negative	*	*	*	*
50	negative	*	*	*	*
51	negative	*	*	*	*
52	negative	*	*	*	*
Average 25 out of 52 positive passive transfer reactions *(48%)*					
Average: (Oral)		21 positive (84%)			
Average: (Parenteral)			20 positive (80%)		
Average: (Oral)				2.6	
Average: (Parenteral)					2.6

*Subjects who were not good passive transfer subjects not figured in average.

PROCEDURE

Serum from a ragweed-sensitive donor was injected intracutaneously into the ventral surface of the right forearm. The serum of the summer-grasses-sensitive donor was injected in the same manner in the left forearm. In each case .05 c.c. of serum was used. These sites were encircled with indelible ink for identification.

The passive transfer subjects were divided into two groups. Twenty-four hours after injection of the donor serum one group received three capsules of processed mixed ragweed, lawn grasses and common pollens (30 mg. in each capsule, a total of 90 mg.) on a fasting stomach. The other group received 1,000 pollen units of the Lederle mixed antigen, subcutaneously in the deltoid region.

The sensitized sites were observed at regular intervals for six hours. Measurements of the erythema were recorded. The greatest response was considered as the index of reaction.

RESULTS

As shown in Table II, there were twenty-five persons out of fifty-two subjects who demonstrated positive passive transfer reactions (48 per cent) either to subcutaneous injection of 1,000 pollen units or to oral ingestion of three processed pollen tablets or both.

Of the twenty-five who showed positive passive transfer reactions, twenty-one (84 per cent) showed passive transfer reactions following the ingestion of the processed oral pollen antigen. The average time required for the development of the greatest response was 2.6 hours.

Following injection of the commercially produced Lederle antigen, twenty of these subjects (80 per cent) showed positive transfer reaction. Development of the greatest reaction required an average of 2.6 hours.

CONCLUSIONS

Controlled passive transfer tests have demonstrated effective absorption by oral route of processed pollen antigens.

The dosage of mixed processed antigens used orally (90 mg.) has demonstrated an effect equivalent to 1,000 pollen units of parenteral antigen.

The time interval to the height of reaction was the same for oral as for injected antigen. This suggests that the antigen response depends on a mechanism which is independent of the route of introduction of the antigen.

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THE NATURE OF BENADRYL ACTIVITY AND ITS CLINICAL APPLICATIONS

THOMAS H. McGAVACK, B.A., M.D., F.A.C.P.
New York, New York

IN an analysis of several benzhydryl alkamine ethers, which Rieveschl prepared, Loew, Kaiser and Moore[9,10] found beta-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) and beta-piperidinoethyl benzhydryl ether hydrochloride to have equally high bronchodilator and antihistamine properties in small laboratory animals.

Benadryl was selected for extensive clinical trial.* However, before using it in diseased states, we administered the drug to more than 100 healthy human subjects in an effort to elucidate further the scope of its action and to detect any signs of toxicity from therapeutically active doses. Methods[12,13] and the majority of the results in the normal subjects and in approximately 400 patients[4,5,6,7,12,13,14,15,16,17] have been reported previously. A brief summary and critical analysis of these data may be of value in the further application of Benadryl clinically.

SUMMARY OF DATA

Pertinent to the influence of the drug on healthy human subjects are the observations of its effects on gastric acidity, blood pressure, pulse rate, the eye, capillary permeability, glucose tolerance, the central nervous system, and the dermic responses to histamine. In Table I, the number of subjects involved, the minimum dosage level at which effects have been noted, and the character of the maximum effect obtained are noted. Moreover, the probable nature of the reaction in each instance is schematically suggested.

One of the most consistently demonstrated effects of Benadryl has been its ability to suppress *flare and wheal responses of the skin to histamine* introduced locally.[1] This influence has been observed in at least three ways. In thirty-six subjects, Benadryl was applied topically as an ointment in strengths of 2 and 5 per cent, respectively, before, together with, and after the introduction of histamine. In all instances, in which the ointment has been rubbed in a few minutes before or at the time of application of histamine, there has been complete protection from its action. If the ointments were applied from 0.5 to 4 minutes following the percutaneous application of histamine, some measure of effect was still observed. With the 2 per cent strengths, a reduction in the wheal-flare reaction was slight, averaging about 15.3 per cent for seven subjects tested. However, itching

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TABLE I. NATURE OF THE ACTION OF BENADRYL IN HUMAN BEINGS

Test of	No. Subjects	Min. Dose Level for Effect*	Maximum Result	Probable Nature of Reactions†			
				Sympatho-mimetic	Atropine-like	Hyoscine-like	Anti-histamine
Histamine	27	150 O/D	Complete suppression	?			++++
skin response	36	2%					
Gastric acidity	32	150 O/D	Complete suppression	?	+	±	+++
Blood pressure	74	400 O/D	Decrease orthostatic hypotension	—	—	+	
	14	30 I.V.					
	14	400 O					
Pulse rate	88	?	—	—	—	—	
Eye	60	0.5%	Mydriasis	++++	++++	++++	
			Loss accom.	—	++++	++++	
			Antagonizes eserine	++	++++	++++	
			Synergist—epineph.	+	+	+	
			atropine	+++	+++	+++	
Capillary permeab.	28	150 O/D	40% decrease				++++
Glucose tolerance	14	400 O	No change	?	?	?	
	14	30 I.V.	Increased	—	?	?	
Sensorium	242						
	105	50	Drowsiness	—	—	++	
	67	150	Dryness mouth		++++	++++	
	5	400	Loss memory	—	±	++	
	5	400	Incoordination		±	++	

*O/D=Orally per day
I.V.=Intravenously
O=Orally, unit dose
%=Ointment (skin) or watery solution (eye), containing Benadryl in the per cent indicated by the numeral
†All responses graded as — to + + + +, representing degrees from "no effect" to maximum response

was relieved in all. With the 5 per cent ointment, the reaction was reduced to as little as 5 per cent of the control size, and for thirty-six subjects showed a test site 32 per cent of that of the control. The entire reaction was shortened to approximately six minutes by this treatment.

In twenty-seven subjects, 300 mg. or more of Benadryl were given daily *per os* for periods of three weeks or more. Weekly tests showed a gradual diminution in the reaction of the skin to histamine. At the end of the period, in more than 50 per cent of the subjects there was a complete suppression of the response to percutaneously administered histamine, while in the remainder of the subjects this effect was materially reduced.

No change in the response of the skin to histamine was noted following a single intravenous injection of 10 mg. of Benadryl; tests were done at hourly intervals for four hours following the injection; therefore, an early effect could have been missed.

The concentration of *free and total acid in the gastric contents* was determined at weekly intervals for from three to eight week periods in thirty-two subjects who received from 150 to 400 mg. of Benadryl daily. The effects were slight at the 150 mg. per day level, and the drug had to be continued not less than ten days for these to appear. In the first nineteen cases, a pronounced decrease in both free and total acid content was observed after two to three weeks of treatment; occasionally the value for the free fraction reached zero. In Case 20, and in three of the remaining twelve cases, an actual increase in acidity was observed, which was maintained on repeated tests so long as the drug was continued. In one patient,

the level of gastric acid was not altered by five weeks of treatment with 600 mg. of the drug daily.

The *blood pressure* and *pulse rate* of seventy-four patients were taken at daily or more frequent intervals, while they were receiving daily doses of Benadryl ranging from 150 to 600 mg. No change in pulse rate was noted at any level of dosage. Forty-five of the seventy-four patients showed a slight lowering of systolic blood pressure, usually not apparent until 300 mg. of the drug had been used daily for three weeks or more; orthostatic hypotension occurred in five. Details are given elsewhere.[13]

Mydriasis and loss of accommodation occurred in more than 75 per cent of the patients into the *eyes* of which Benadryl was instilled in 0.5 per cent solution, according to a technique already described.[7] In these experiments Benadryl acted as a synergist of epinephrine and atropine and as an antagonist to eserine.

A distinct diminution in *capillary permeability*, as measured by the fluorescein technique,[8] was observed in seven of eleven patients who had received Benadryl, 150 mg. daily for periods of three weeks or more. Decreases ranging from 10 to 65 per cent with an average of approximately 40 per cent were seen in fifteen instances in which 300 mg. or more of the drug were given daily for three weeks or more.

A unit dose of 400 mg. of Benadryl failed to alter *glucose tolerance* in any of fourteen patients.[16] When 30 mg. were given intravenously, sugar tolerance was definitely although not strikingly increased. In the course of treating 242 patients for various diseases with Benadryl, 131 showed some "side reaction" at some level of dosage between 50 and 600 mg. daily.[13] In 380 analyses, the frequency of symptoms which pointed commonly to disturbances of the sensorium included: drowsiness, observed in 105 instances (27.6 per cent); dryness of the mouth in sixty-seven (17.6 per cent); dizziness in fifty-four (14.2 per cent); weakness and easy fatigability in thirty-six (9.5 per cent); in-co-ordination and light headedness in eleven (2.9 per cent); blurring of vision in ten (2.7 per cent); and loss of memory in three (0.8 per cent).

PROBABLE NATURE OF THE ACTION OF BENADRYL

The nature of the observed effects of Benadryl has been suggested in Table I. It is our belief that the influence of the drug upon capillary permeability and the response of the skin to histamine is solely due to a direct blocking effect upon that drug within the tissues. The depression of gastric acidity is probably due not only to this same action but also to an influence upon the autonomic nervous system via an atropine-like action upon the vagus. Such a concept is in line with the investigations in dogs carried out by Loew, MacMillan and Kaiser.[11] Furthermore, the interplay of two or more factors may explain the reversibility and inconstancy of the action.

The failure to raise the pulse rate or blood pressure, even transiently,

the tendency to an increased rather than a decreased glucose tolerance, and the frank soporific effect upon many subjects, all seem to rule out a sympathomimetic effect as the basis for Benadryl activity.

Alterations in the function of the eye following the topical application of Benadryl are clearly those which may follow the application of alkaloids of the belladonna group. Were this effect like that of atropine one would expect to find an increase in the pulse rate and blood pressure, at least in the acute experiments. On the contrary the blood pressure was frequently lowered and the pulse rate not changed. Such findings are more compatible with a hyoscine-like action. Such a type of effect seems all the more likely when the changes in the sensorium are considered. The drowsiness, dryness of the mouth, weakness, easy fatigability, loss of memory and in-co-ordination, when taken together, simulate the influence of scopolamine rather than that of atropine.

From these pharmacologic and pharmacodynamic studies, we have concluded that *the action of Benadryl is a composite one, in which both antihistamine and hyoscine-like effects are prominent.*

DOSAGE IN RELATION TO THE INDIVIDUAL

The antihistamine effect of Benadryl is always predominant and is apparently a quantitative matter. However, the susceptibility to both the antihistamine and hyoscine-like actions is extremely variable from person to person, and in the same subject from time to time. It is therefore important always to individualize the dose of the drug employed. Since the action of a single orally administered dose reaches its peak in from forty-five to ninety minutes and is probably completely over within four hours, it is important to distribute the total daily dose as evenly through the twenty-four hours as possible. In actual practice, an even division of the waking hours is employed. In general, 150 mg. daily is the initial amount. When it is necessary to give 250 mg. (five capsules of 50 mg. each) 100 mg. is given at bedtime. If the patient is awakened because of the condition for which Benadryl was given, an additional dose of the drug may be taken at that time. If more than 400 mg. is needed daily, then a single capsule (50 mg.) every two hours is more effective than larger doses less frequently.

Our comments on dosage thus far have referred to the orally administered drug. In some instances, the route of administration is important. For example, in Ménière's syndrome, migraine, and angioneurotic edema, a very rapid action is commonly desirable. Thirty mg. or less in aqueous solution may be given safely intravenously in such instances. This may then be followed by oral administration when practicable.

In certain itching dermatoses it is often important to obtain a maximal local effect with a minimal systemic action. Here a 2 per cent ointment has frequently proven highly effective. The application may be repeated

as frequently as necessary to control the symptoms, for the degree of systemic absorption by way of the skin is slight.

While side reactions to Benadryl are common, occurring in slightly more than half of the patients,[13] they have been so mild as to preclude the continued use of the drug in only 0.8 per cent of all patients. Their incidence is relatively highest when 150 mg. of drug are used per day. This is chiefly due to the fact that most patients are started at this level of dosage.

Drowsiness is the most commonly observed unpleasant symptom and, like all of the other side reactions, usually makes its appearance following the first or the first few doses of the drug. A tolerance seems to be rapidly built up against these side reactions, even if the patient is continued on the same dose of drug. However, it is our custom to reduce the daily dose by one-third when such symptoms appear. As soon as they have disappeared completely, which takes from one to seven days as a rule, the dosage can usually be increased without further distress. In this way we have been able on a number of occasions to administer without side effects 600 mg. daily to individuals who developed "irresistible" sleepiness following the first dose of the drug. In only five patients have symptoms been so severe or so persistent as to necessitate discontinuing the drug completely.

In those patients who experience drowsiness or other unpleasant symptoms during the first days of treatment, there is no contraindication, as far as Benadryl is concerned, to the use of black coffee, or amphetamine, the latter in doses of 2.5 to 5.0 mg. Either or both of these agents may be used and both are effective against the unwonted sleepiness.

DOSAGE IN RELATION TO THE DISEASE

Inasmuch as the variation in activity may depend at least in part upon the amount of histamine released in various morbid states, the nature of the disease to be treated will materially influence the dose selected (Table II). For instance, in an analysis of 242 patients[13] we have found that the largest doses are usually required for those conditions in which widespread allergic manifestations are present, as, for example, urticaria, neurodermatitis, asthma, and so forth (Table II). When sedation is desirable it is equally important to use the larger doses, for the hyoscine-like activity of the drug is weaker than its antihistamine effect. We refer to patients with intractable insomnia, generalized pruritus from any cause, functional dysmenorrhea, and so forth.

Mainly because of its antihistamine effect, we have found the drug valuable in the majority of cases of angioneurotic edema, generalized pruritus, urticaria, "allergic eczema," hay fever, vasomotor rhinitis, and uncomplicated types of asthma (prophylactically) (Table II). Both its antihistamine and hyoscine-like actions seem to have been useful in neurodermatitis, in certain cases of asthma, migraine, cardiac asthma, essen-

tial hypertension, functional dysmenorrhea, spastic colon and other gastrointestinal neuroses, but the percentage of favorable results is much lower than for the group of conditions mentioned just above.

As soon as any one of these conditions is fully controlled, the amount of the drug given daily may be cautiously reduced. If there is at any time a recurrence of symptoms, no matter how mild, during the "reduction phase" of the treatment, the next highest dosage level should be resumed for a few days. By following this dictum, patients with bronchial asthma have been maintained symptom-free over long periods of time (up to twenty months thus far) on dosages as high as 400 mg. daily. There are apparently no ill effects from the drug at this or even higher doses for considerable periods of treatment.

TABLE II. AVERAGE DAILY DOSE OF BENADRYL IN SEVERAL DISEASES

Condition	Average daily dose (mg.)	Unimproved (per cent)
Migraine	100 (U)*	30.0
Hay fever	150	25.0
Vasomotor rhinitis	150	27.2
Meniere's syndrome	150	40.0
Intractable insomnia	150 (U)*	44.4
Spastic colon	200	26.7
Generalized pruritus	250	0.0
Functional dysmenorrhea	250	21.1
Angioneurotic edema	300	10.0
Allergic eczema	400	50.0
Neurodermatitis	400	66.7
Bronchial asthma	400	30.4
status	600	
Cardiac asthma	600	50.0
Urticaria—acute generalized	600	8.3
—chronic	300	

*U—Unit dose; in cases with insomnia this is given from 15 to 45 minutes before retiring.

COMPARISON OF BENADRYL WITH OTHER ANTIHISTAMINIC SUBSTANCES

A priori, it might have been thought that other members of the series of drugs studied in animals would equal or even surpass Benadryl in therapeutic activity. In regard to antihistamine death, Benadryl and a closely related compound, beta-morpholino-ethyl benzhydryl ether hydrochloride, proved equally active, whereas the latter, while showing no side reactions in the human being except in the largest doses, is less than half as active therapeutically. N-pyridil-N-benzyl-N-dimethylethylenediamine (Pyribenzamine), believed to be about seven times as effective as Benadryl in preventing death from histamine in animals,[2] while by no means exhaustively compared with Benadryl, appears to be no more effective weight for weight in allergic states in man. Examples could be further multiplied but would serve no further purpose in emphasizing the necessity for trying each of these agents extensively in healthy human subjects and patients with allergic diseases before making final decisions as to their applicability and relative merits.

Benadryl has been the subject of the most exhaustive surveys thus far made with any of this general group of drugs. It has not as yet been extensively or intensively compared clinically with closely related compounds. Although Feinberg[2] has inaugurated such an effort, full details of his experiments, i.e., dosage, dosage interval, periods of trial and so forth, are as yet not fully elaborated. Insofar as such data are available,[3] the comparisons appear for the most part to have been made between daily doses of 150 to 200 mg. of Benadryl and 200 to 400 mg. of Pyribenzamine. In the light of present knowledge, such comparisons probably will not afford a true basis for analysis.

Our own meager opportunities for comparisons raise the possibility that no one drug will surpass *all* others in therapeutic applicability to *all* allergic or closely related diseases, but that one may serve a better purpose in one instance, another in a second, still a different one in a third, and so on.

SUMMARY

It seems quite clear that the benzhydryl alkamine ethers have found a definite place in the treatment of allergic diseases that depends predominantly upon their ability to block quantitatively the action of histamine in the tissues. In the case of Benadryl, a second weaker hyoscine-like action enhances the value of the drug where a mild sedative as well as an antihistamine effect is desirable.

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RHEUMATOID ARTHRITIS—FOOD ALLERGY AS A FACTOR

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THERAPEUTIC EFFECTS OF CERTAIN ANTIHISTAMINE DRUGS IN ALLERGIC CONDITIONS

(Continued from Page 214)

same effect clinicallly. The writer gains the impression that possibly Histadyl and Pyribenzamine are a trifle better than Hydryllin and Benadryl, but not sufficiently so to warrant a definite statement to that effect. In those cases of bronchial asthma associated with pollinosis, Hydryllin appeared to be more efficient than the other preparations. Compound 1695 was not as effective as the others in our hands.

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700 East Jefferson Street
Syracuse, New York

THE ROLE OF STREPTOCOCCI IN BRONCHIAL ASTHMA

Etiologic Significance and Treatment with Streptococcus Filtrates

HERMAN A. HEISE, M.D.
Milwaukee, Wisconsin

ROLE OF BACTERIA IN ALLERGIC DISEASES

THE etiologic role of bacteria in allergic diseases is doubted by some allergists. Their opinion is based upon failures in the use of bacterial antigens for treatment. These failures can often be ascribed to one or more of the following conditions: (1) nonspecific bacterial preparations may have been used; (2) the preparations may have been so modified by repeated reculturing[5] or altered by heat or chemicals that their antigenicity is lost; (3) the use of bacterial vaccines containing organisms for treatment when the active principle may be a *soluble* bacterial product; (4) the mechanism of immunity[6] in allergy is not understood, so that the physician may rely too much upon skin and passive transfer tests, which are not necessarily characteristic of the local tissue immunity of allergy.[7] Also, there are some who believe that desensitization always involves the overwhelming of the patient with antigen so as to neutralize his fixed antibodies.

Most bacteria owe their primary pathogenesis not to toxic by-products but to the ability of the body cells to produce specific antibodies, which, in their effort to destroy the nontoxic antigen, are involved in an antigen-antibody conflict which may react unfavorably to the body cells which harbor the antibodies. In other words, the *defense* is more destructive than the invasion, and it must be remembered that it is the allergic individual who owes his downfall to an overly sensitive immunity mechanism, which provokes a conflict against ordinarily innocuous substances. As far as the immediate effects of inflammation are concerned, it would be better for the body to ignore the invader than to fight him. Notable exceptions are diseases caused by Cl. botulinum, Cl. tetani, and C. diphtheriae, all of which owe their pathogenesis to true toxins. The incubation period of a disease is not necessarily the time for bacteria to gain in numbers and virulence sufficient to start the battle, but usually is the period in which the defense mechanism has gained enough power to engage the invader in an antigen-antibody struggle. The incubation period is short when the immunity is high, and longer when the immunity is low or absent. The ordinary bacteria which are universally present in the upper respiratory passages of man develop pathogenic significance only when the local antigen-antibody reaction is exaggerated by the altered reactivity of the patient. The analogy of the action of nontoxic bacterial products and ordinary allergens seems evident.[1] There appears to be but one immunity mechanism, which has been created for the *protection* of the individual. "It is neither

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Dr. Heise is an Associate Fellow of the American College of Allergists.

paradoxical nor surprising that a mechanism, which in natural circumstances tends directly towards immunity, should react to the disadvantage of its possessor when exposed to a stimulus that formed no part of the environment in which it was evolved."[7]

STUDY LIMITED TO EVALUATION OF STREPTOCOCCUS FILTRATES

Although I have used vaccines with varying degrees of success and failure, the discussion in this paper will be limited to the use of streptococcus filtrates and presents an analysis of the results obtained in a selected group of 328 persons who were treated with autogenous or stock bacterial filtrates. The study was begun twenty years ago and involves more than 10,000 cultures. Those patients whose asthma was caused obviously and solely by extrinsic factors were excluded from this survey. The group did include those in which foods were suspected of being etiologic factors, as well as persons who had had thorough allergic study and whose symptoms persisted in spite of elimination of foods and inhalants. Food factors were purposely ignored in order to evaluate properly the results obtained by the use of the bacterial filtrates alone.

The use of bacterial filtrates in the treatment of asthma is not new. Wilmer[9] made use of filtrates from a 1 per cent solution of sterile dextrose which had been inoculated with chunks of sputum. In accordance with a suggestion made to me by Eiman in 1927, I inoculated tubes of broth with sputum and after incubation prepared filtrates. Some good therapeutic results were obtained when the autogenous filtrates were injected subcutaneously. However, there were some definite disadvantages. Many of the filtrates had an objectional "dead tooth" odor and some produced violent asthmatic attacks shortly after injection. It was evident that some of the filtrates contained a powerful antigen, and this study was directed toward its identification.

A study of sputum cultures of a number of asthmatic patients brought to light the fact that the chief organism seen was a streptococcus. It was therefore considered advisable to make pure streptococcus filtrates, discarding any other organisms found in the original culture. Later it became evident that streptococci isolated from the sputums of asthmatic patients, particularly those obtained from children, frequently produced filtrates of tremendous potency, which, on injection in minimal quantities of the undiluted material produced violent asthmatic attacks. Such filtrates were used as "stocks" and represent the usual type of treatment employed in most of the cases discussed in this paper. Filtrates prepared from the other organisms found in sputums neither aggravated asthma nor were they of value in treatment.

PREPARATION OF FILTRATE

The filtrates, whether autogenous or stock, which have been used on all the patients in this series are made as follows: sputum or throat culture

swabs are streaked upon large slants of Bacto Brain Veal Agar* so that indvidual colonies can be isolated. After trials with various media, this particular medium,[3] which was devised for the gonococcus, has proved to be ideal for the growth of the streptococci desired. The tiny "dew drop"

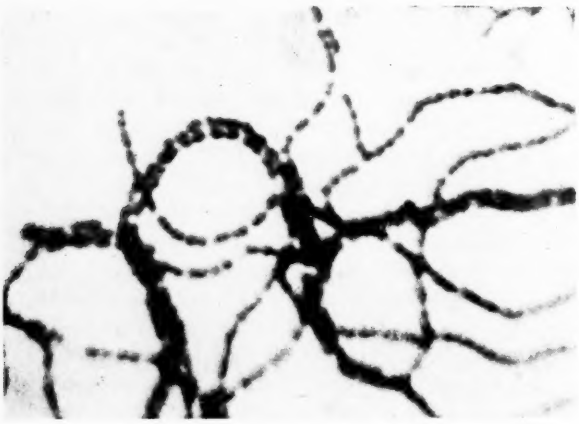

Fig. 1. A streptococcus which produced a potent filtrate.

colonies of relevant streptococci are easily recognizable after about fifteen hours of incubation. From such colonies, tubes of broth are inoculated (Bacto Nutrient Broth,* to which is added, as suggested to me by Eiman, 0.5 per cent each of sodium chloride and dextrose, several small pieces of calves' brain, and marble chips). A deep tube is essential so that different degrees of oxygen tension are provided, and so that conditions for growth may be optimal in some part of the tube. After the fourth day of growth, the culture is examined to confirm purity of the organism, the broth is filtered through a Seitz disc, and the filtrate tested for sterility. The filtrate containing the unchanged, soluble bacterial protein is diluted with buffered saline solution, and is then ready for use. Standardization does not depend as much on the antigen as it does on the degree of allergic reactivity of the patient, since the filtrate itself is nontoxic. All that is necessary is to commence treatment with a 1:1,000,000 dilution and double the dosage until therapeutic results are satisfactory, or until it is evident that the filtrate is of no value for that particular patient. Experience has indicated that focal reactions with a 1:1,000,000 dilution are rare, so that an injection of about .02 c.c. of this dilution is a safe amount for starting treatment. Occasionally, however, a greater dilution is necessary in order to avoid unfavorable reactions. Skin tests are occasionally positive, but cannot be relied upon to diagnose the hypersensitivity of the tissues of the lungs.

*Difco Laboratories, Detroit, Michigan.

TABLE I. PROGNOSTIC VALUE OF CHANGES IN LENGTH OF STREPTOCOCCI ON RECULTURING

	Number of Individuals Tested		Ratio A:B
	Improvement of Symptoms (A)	No Improvement (B)	
Chains becoming shorter on reculturing	56	8	7:1
Chains becoming longer or remaining of same length on reculturing	23	49	1:2

CULTURAL CHARACTERISTICS AND MORPHOLOGY OF ORGANISMS

On blood agar the colonies exhibit alpha hemolysis, placing them in the viridans group. The morphology of organisms producing filtrates of the highest potency is worthy of mention. In four-day broth cultures, the chains are often found to be unusually long and have a tendency toward parallel grouping (Fig. 1).

This characteristic morphology is interesting, since the finding of long-chain streptococci has usually assured a good prognosis for the individual who harbored the organism. On the other hand, repeated failure to isolate characteristic streptococci has been associated with a poorer prognosis, and the corresponding filtrates have been of doubtful value when used as "stocks." The most striking finding was the fact that successful autogenous immunologic treatment was usually associated with a subsequent shortening of the chains of streptococci found in throats, and that relapses were usually associated with a subsequent lengthening of the chains (Table I).

NATURE OF FILTRATE

The filtrate contains a bacterial product which is destroyed by boiling. This has been repeatedly demonstrated by the failure to produce reactions or improvement when the boiled filtrate was injected into susceptible persons. An unboiled filtrate has been kept in a refrigerator with no demonstrable loss of potency in nine years. The experience with this filtrate is especially interesting. It was prepared in 1935 from the throat of a three-year-old girl whom I was able to observe daily. At that time the diagnosis of bronchopneumonia was made because of fever and dyspnea, although the lungs remained emphysematous. After the acute phase, lasting for several days, the asthmatic râles persisted. A pure culture of alpha long-chain streptococci was obtained from her throat, and the filtrate diluted 1:1,000,000 was used for treatment. This was followed by sudden disappearance of the asthma. Within the last ten years the same filtrate has been used for the child on several occasions, the last being in 1944. Each time the chest had "tightened" with a cold, and relief followed within a few hours after an intracutaneous injection of

TABLE II. DISTRIBUTION INDEX OF STREPTOCOCCI WITH REGARD TO LENGTH OF CHAINS

Condition	Number of Cases	Average Length of Chains (L)	Ratio, No. Strep. to Other Bacteria (N)	Length Distribution Index (L x N)
Intrinsic Asthma	211	2.6	3.0	7.8
Rhinitis and Sinusitis	105	2.1	2.5	5.3
Arthritis	21	1.8	2.6	4.7
Bronchitis	19	1.9	2.3	4.4
Recurrent Colds	39	1.7	2.4	4.1
Angioneurotic Edema	26	1.7	2.6	4.4
Extrinsic Asthma	15	1.6	2.5	4.0
Normal	22	1.7	2.5	4.3

.02 c.c. of a 1:1,000,000 dilution. On the other hand, an injection of .02 c.c. of a 1:10,000 dilution regularly aggravated the condition. This filtrate was used in about 100 of the 328 persons discussed in this survey. Normal individuals fail to notice more than a slight local reaction even when enormous doses, e.g., 0.5 c.c. of an undiluted filtrate, are used. On the other hand, some patients are so sensitive to the preparation that severe asthma can be expected from injections unless minimal doses are used. These facts suggest that we are dealing with a nontoxic bacterial product which is capable of producing allergic reactions.

SPECIFICITY OF THE STREPTOCOCCUS FILTRATE

Although no proof of specificity has been obtained, it is evident that the streptococci isolated have an important antigenic factor in common. This has been demonstrated by the therapeutic value of stock filtrates. In a series of about twenty patients who were treated with the Dick streptococcus filtrate, no equivalent results were obtained. Evidence against specificity is my observation that the arthritis, which so frequently occurs in patients suffering from asthma, has occasionally been favorably influenced by the use of the filtrates. This finding adds weight to the prophetic statement from Rackemann:[4] "The solution of the arthritic problem must inevitably help the asthma problem and *vice versa*." Although streptococci were found in practically every throat examined, some significant differences in the chain-length incidence patterns in various diseases were found. By classifying the streptococci on the basis of *length* of chains from 1 to 4-plus, and the relative *numbers* of streptococci on a similar basis, Table II was obtained. This table indicates greater incidence and longer chains in cultures from untreated intrinsic asthma, compared with a similar study of other conditions.

TECHNIQUE OF TREATMENT

It must be emphasized again that this survey was undertaken to evaluate the importance of the streptococcus filtrate, and that the treatment outlined here is not to be considered to be ideal for all patients. The experimental treatment consisted of the intradermal injection of extremely small

doses of filtrate. If aggravation of symptoms occurred, the dose selected was probably too high, and a much greater dilution was prepared for the next treatment. It must be emphasized that an earnest attempt was made to avoid focal reactions by proper regulation of dosage, and that the

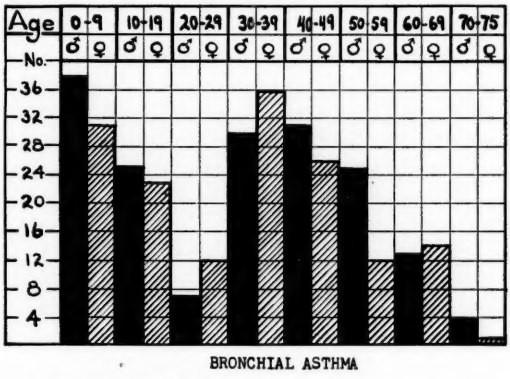

Fig. 2. Analysis of 328 patients arranged according to age at the time of starting treatment.

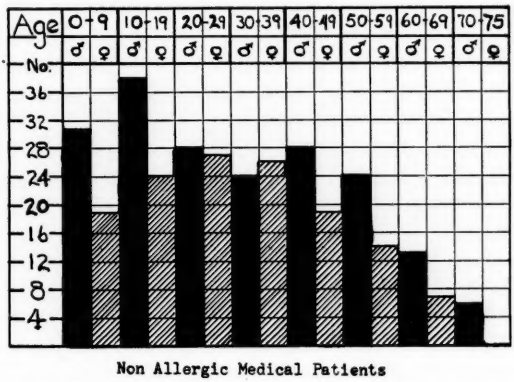

Fig. 2a. Control chart prepared under conditions exactly as in Figure 2.

object of treatment was to inject ascending doses of antigen, which could be localized in the skin without stimulating the shock tissue in the lung.[2]

The usual experience, then, was improvement which began within several hours after each injection. Most patients have volunteered the information that they felt sleepy for several hours after the injection, then felt better for several days, after which they again had some increase in symptoms. Further injections usually caused a repetition of the cycle, although the languor became less and less noticeable. The problem then became one of establishing the interval between injections to avoid the

phase of return of symptoms. The interval between injections could usually be lengthened gradually from one day to a month or more. The dosage was usually doubled each time if there were no unfavorable reactions. However, the best results were obtained by avoiding the prin-

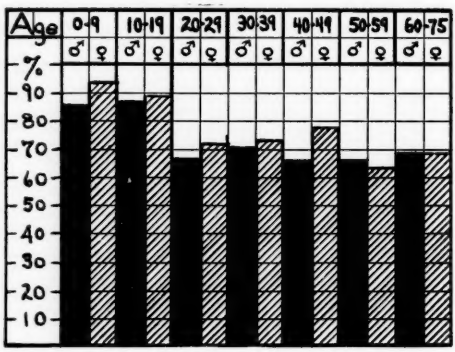

Fig. 3. Analysis according to percentage improvement in age groups.

ciple of trying to give the patient as much as he could stand. Continual increase of dosage in a symptom-free patient often caused relapses. The original dose was usually .02 c.c. of a 1:1,000,000 dilution, and it was rarely necessary to use a dilution stronger than 1:1,000.† Relapses occurring a year or more after stopping treatment are of common occurrence. However, resumption of treatment with minimal dosages is usually followed by prompt improvement. When there was doubt as to the role played by the diluted filtrate in producing or aggravating asthma, control injections of the diluent only were given without the patient's knowledge. These experiments usually confirmed the role of the streptococcus filtrate in producing reactions.

RÉSUMÉ OF RESULTS IN THE USE OF STREPTOCOCCUS FILTRATE

A survey of patients classified as to age at the onset of treatment is important, since it confirms the well-known fact that there are natural tendencies to recover from asthma at certain ages. This fact must be considered before one claims too much credit for any particular type of treatment. The data for Figure 2 were obtained from the Allergy Clinic at the Milwaukee County Hospital. The control chart (Fig. 2a) was prepared under exactly similar conditions, except that only nonallergic medical patients were considered.

Figure 2 clearly indicates that the tendency toward spontaneous recovery is responsible for the small number of patients in the age group of twenty

†A practical method of labeling bottles has been to designate a 1:1,000,000 dilution as 6, 1:100,000 as 5, 1:10,000 as 4, 1:1,000 as 3, 1:100 as 2, the rationale being logarithmic designation omitting the minus sign.

TABLE III. AVERAGE IMPROVEMENT IN AGE GROUPS

Age	0-9	10-19	20-29	30-39	40-49	50-59	60-69
Males	86%	87%	67%	71%	66%	66%	69%
Females	94%	89%	72%	73%	78%	64%	69%

TABLE IV

Age Groups	Number of Patients	"Cured"	Improved	Unimproved
0-9	69	45	23	1
10-19	48	27	19	2
20-29	19	4	13	2
30-39	66	23	37	6
40-49	57	18	34	5
50-59	37	6	28	3
60-69	27	3	20	4
70-75	5	1	3	1
Totals	328	127	177	24

to twenty-nine. Beyond this age group, the incidence of asthma rises up to the age of forty, after which there is a decrease in the number of patients with advancing years. The chart also throws light on the poorer prognosis after the age of twenty, as shown in Figure 3.

In order to evaluate some of the factors involved in the treatment, it was found practicable to estimate the per cent of improvement in each case based upon such factors as duration and severity of symptoms, amount of palliative treatment necessary, and, particularly, the improvement at certain seasons of the year as compared with the same seasons of previous years. By using these criteria, some interesting comparisons are possible, which are given in outline form in Table III.

This information is graphically presented in Figure 3. These figures should not be used for comparison with other methods of treatment. Investigators of other methods have used other criteria in choosing their patients, while this survey was limited to the use of a single therapeutic agent in a carefully chosen group of patients. The figures are significant only insofar as they indicate differences in prognosis in the various age groups in this survey. Figure 3 indicates that the prognosis is excellent in persons under twenty, improvement averaging 89 per cent, while the improvement remains at about 70 per cent in all age groups over twenty. Some of the improvement in children can be attributed to a natural tendency to recover, but the immediate improvement which usually occurs after treatment cannot be ascribed to "immunologic maturation." The reason for the poorer prognosis in older people appears to be the presence of complications, such as inhalant factors, tuberculosis and heart disease, and actual lung damage, such as fibrosis, bronchiectasis or emphysema.

Table IV presents an analysis of the 328 patients according to a commonly used criterion. All investigators who have made similar surveys realize that this is but a "snapshot" of a quickly moving picture, and cannot be accepted as the final disposition of the individuals.

IMPORTANCE OF EXTRINSIC ALLERGENS

Excellent results were obtained when the filtrate alone was used as treatment. Although food tests were frequently performed, the patient was not informed of the result, in order that the efficacy of the filtrate alone could be determined. Patients who believed that certain foods caused trouble were advised to continue avoiding them. However, after treatment with the filtrate, the patients have usually volunteered the surprising information that foods which had previously caused attacks of asthma no longer had this effect. A similar experience was observed regarding certain physical factors, such as cold air, exercise, et cetera. There was, however, one notable exception to this rule. The reactivity to inhalants was not influenced by the filtrate therapy. This fact is extremely important, because failures in treatment are often attributable to sensitivity to inhalants. Symptoms of asthma often returned during the fall hay-fever season but immediately cleared up with the coming of frost, although some of the patients had never before been symptom-free during the winter, spring, and summer months. It is therefore important not to overlook the inhalant factors, and to inform those patients whose asthma is complicated by pollen sensitivity that relapses are to be expected unless the pollen factor is successfully combated. From this study it appears that the most important factors in causing asthma are those *which come into direct contact with the tissue of the lung,* such as bacteria and inhalants. Bacteria are particularly important because they are self-propagating and are responsible for the numerous examples of the continuation of pollen asthma after the disappearance of the pollens which originally caused the asthma. The food factor need not be ignored, since foods may definitely upset the "allergic equilibrium" which has been so clearly discussed by Vaughn.[8] However, this study indicates that the balanced allergic state can usually be restored by directing the treatment against the bacterial and inhalant factors alone. This finding is extremely important, since many patients, children particularly, will be better nourished and less neurotic if the diet is not too greatly curtailed. This experience parallels that obtained in the treatment of hay fever and pollen asthma, in which food factors may be of importance only while the pollen factor is not controlled.

Finally, the analysis revealed that the ideal patient for this form of treatment proved to be the child whose asthma started after a cold, or was aggravated by colds, and whose asthma was definitely worse in winter than in summer, or the individual who had had an adequate allergic study and treatment without improvement.

The following case history concerns the experimental treatment of one of the asthmatic patients whose treatment was purposefully limited to the use of bacterial antigens.

CASE REPORT

M. H., aged fifty-seven in 1935, complained of sneezing and clogging of her nose since 1929, wheezing and coughing since 1931. The first attack of asthma followed a cold, and all attacks were caused or aggravated by colds. All foods agreed. Attacks occurred about once a month during the winters and were extremely severe, requiring hospitalization several times. Attacks were worse in winter. Previous skin tests had revealed positive tests for wheat, but she was no better after having been on a wheat-free diet. Her own cultures from the nose revealed staphylococcus 4 plus, and a sputum culture revealed chiefly long-chain streptococci. Treatment was begun November, 1935, and consisted of weekly intracutaneous injections of a stock streptococcus filtrate 1:1,000,000 to 1:100,000. Occasionally aggravation of symptoms occurred within twenty-four hours after a treatment. Under these conditions the next dose was cut back. After six months of treatment, the asthmatic attacks ceased. However, the nasal condition had not improved. At this time an autogenous vaccine containing the nasal staphylococci, 100 million per c.c., was combined with a 1:1,000,000 filtrate from the long-chain streptococci found in the throat. This antigen was used, starting with .02 c.c. and proceeding as before. Within one more year the nasal condition had cleared up and there was no more asthma, and all treatment was stopped. In March, 1938, she returned for treatment. At that time she was under great emotional strain, and although there was no asthma, her chest became "tight" occasionally. Two injections of .05 c.c. of 1/1,000,000 stock streptococcus filtrate were given at intervals of two months. There has been no asthma or nasal trouble to the present time, January, 1948. No dietary restrictions were imposed at any time since the start of treatment.

SUMMARY

A filtrate prepared from the alpha streptococci found in the sputa of throats of many asthmatic patients has been found to be a potent antigen in producing attacks of bronchial asthma, and in high dilutions is an effective agent in treatment.

The length-distribution index of streptococci in intrinsic asthma is greater than in other diseases studied, but bears the closest numerical relationship to the index in sinusitis and rhinitis.

After successful treatment with a streptococcus filtrate the streptococci harbored by the individual are usually of the shorter varieties. Relapses are often characterized by the reappearance of longer chain streptococci.

The streptococcus filtrate has been found to be particularly efficacious in the treatment of chronic asthma in children.

The use of the filtrate has no effect on asthma produced by inhalants, but often prevents the continuation of asthma during the period when these inhalants are not present.

The food factors affecting asthma usually disappear when the bacterial factor is controlled.

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THE EFFECT OF SUBSTITUTION OF ANTISTINE (PHENYL-BENZYL-AMINO-METHYL-IMIDAZOLINE) FOR BENADRYL OR PYRIBENZAMINE DURING THE HEIGHT OF THE RAGWEED POLLEN SEASON

BERNARD DICKSTEIN, M.D., F.A.C.A.
Flint, Michigan

THIS PAPER is a brief clinical report of the effect of Antistine* on a small group of selected patients, all suffering from approximately the same disease, all treated alike, and all exposed to approximately the same amount of the provocative agent.

Although I have been using Antistine in a variety of allergic conditions with fair results, I have not been unaware of the psychological factors resulting in symptomatic relief, especially with the use of new drugs. However, I am inclined to believe that such psychological relief is not too important a factor with patients having severe ragweed hay fever, although it undoubtedly can operate in the mild ragweed-sensitive patients.

With this in mind, the following criteria were used to select patients to receive the Antistine:

1. They must have moderately severe sensitivity, as determined by the severity of the hay fever before treatment and by skin tests.
2. They must be under treatment with injections of ragweed extract.
3. They must exhibit some hay fever symptoms with the pollen count 500 or over.
4. The hay fever symptoms must be controlled to the patient's satisfaction by an average dose, 25 to 50 mg. of Benadryl or Pyribenzamine.

The period of trial started September 3, 1947, with the pollen count about 700, and continued for the next two weeks, during which time the pollen count fluctuated between 600 and 1,100. Up to September 3, 1947, seventeen patients were found to conform to the criteria mentioned above, i.e., they were complaining of hay fever symptoms, had been given either Benadryl or Pyribenzamine, and had expressed satisfaction with the relief afforded.

Antistine was then presented to these patients as another form of the Benadryl or the Pyribenzamine they were already taking, but refined so as to be more effective. The dosage was one or two tablets (100 to 200 mg.) as required for relief, to be taken in exactly the same manner as the previous medication.

Table I is a tabulation of the group and of the results of the trial period.

An analysis of Table I shows that of the seventeen patients, eight were females and nine males. Nine of the seventeen were children. As to severity of disease, nine were classified as "very severe sensitivity," four as "severe," and four as "moderately severe."

All seventeen had some relief with Pyribenzamine, fifteen of these call-

*Antistine used in this trial was supplied through the courtesy of Ciba Co. of Summit, N. J.

TABLE I. TABULATION OF ALL DATA CONCERNED WITH TRIAL OF ANTISTINE ON SEVENTEEN SELECTED PATIENTS

Patient	Age	Sex	Type and Severity	Symptoms	Degree Relief and Side Effects			Patients' Remarks
					Pyriben-zamine	Benadryl	Antistine	
1. T.J.	3	M	H-A ****	A-Sn-C	Rm. O Severe cramps	Rm. No S.E.	Rg-helped A. No S.E.	Antistine best
2. L.G.	5	M	H-A ****	Cat-Sn	Rg. Sleepy	No R. No S.E.	No R. No S.E.	PBZ best
3. Mrs. G.Br	59	F	H-A ****	Cat-C	Rg. DiarrheaO	Helped chest. Rg. No S.E.	No R. Na. & Vom. O	Benadryl best
4. W.F.	28	M	H-A ****	Sn-Cat Occ A	Rg-for Sn-Cat. Listless	Rg. Sleepy	Rsl. Groggy	PBZ best
5. Wm.F.	20	M	H-A ****	Sn-Cat E	Rg. Sleepy	Rg. Sleepy	Rsl-brief. No S.E.	PBZ best
6. S.S.	11	F	H-A **** Br A	Sn-Cat E Occ A	Rg-25mgm Nausea-vomit O	No R. O Sweat-groggy	No R. No S.E.	PBZ better
7. M.Mc.	30	F	H-A **** Br A	Cat-Sn E	Rg-25mgm Listless sleepy	Rg-10mgm Very groggy. O	Rg-50mgm. Sl N	Antistine best
8. G.Br.	26	M	H-A **** All rh	Cat E	Rg. Listless	Rsl. O Very groggy.	No R. No S.E.	PBZ best
9. S.S.D.	7	M	H-A ***	C-Bl Sn	Rsl. No S.E.	Rm. No S.E.	No R. No S.E.	Benadryl best
10. M.G.	29	F	H-A ***	Sn-Bl	Rg-25mgm No S.E.		No R. No S.E.	PBZ best
11. C.W.	39	F	H-A ***	Cat-Sn	Rg. No S.E.	Rg-Sleepy Chest worse. O	Rg. No S.E.	PBZ best
12. I.R.	10	F	H **	Cat-Sn	Rsl. Sl. Nausea	Rm. No S.E.	No R. No S.E.	Benadryl best
13. M.F.	30	F	H **	Cat-Sn Bl	Rg. Nausea	Rg. groggy-jittery O	Rsl. No S.E.	PBZ best
14. G.P.	6	M	H **	Sn-Cat Bl	Rm. No S.E.	Rm. No S.E.	Rg. No S.E.	Antistine best
15. R.K.	3½	M	H **	Cat-Bl	Rg. Groggy		Rg. No S.E.	Antistine best
16. V.N.	20	M	H **	Cat-Sn E	Rg. No S.E.	Rg. Sleepy	No R. No S.E.	PBZ best
17. R.F.	11½	M	H **	E Sn-Bl	Rm. No S.E.	Rm. No S.E.	No R. No S.E.	PBZ slightly better

Explanation of Symbols:

H—Hay fever.
A—Asthma.
Sn—Sneezing.
Cat—Catarrhal symptoms.
C—Cough.
E—Eye symptoms.
M—Male.
Bl—
R—Relief.
Sl—Slight.
M—Moderate.
G—Good.
S.E.—Side effects.
O—Objectionable.
F—Female.
PBZ—Pyribenzamine.
Na & Vom—Nausea and Vomiting.
****—Extremely severe sensitivity.
***—Severe sensitivity.
**—Moderately severe sensitivity.
All. Rhin.—Allergic Rhinitis.
Br A—Bronchial Asthma.

ing the relief "satisfactory." Ten had side effects, chiefly listlessness or nausea; and in three of these ten, the side effects were sufficiently severe to be objectionable.

Thirteen of the group obtained light to good relief with Benadryl, all but two of the thirteen finding it satisfactory. Eight of the entire group

had side effects from Benadryl, chiefly grogginess or sleepiness. One patient complained it made her chest feel tight. Five of the eight having side effects from Benadryl thought them sufficiently severe to be objectionable.

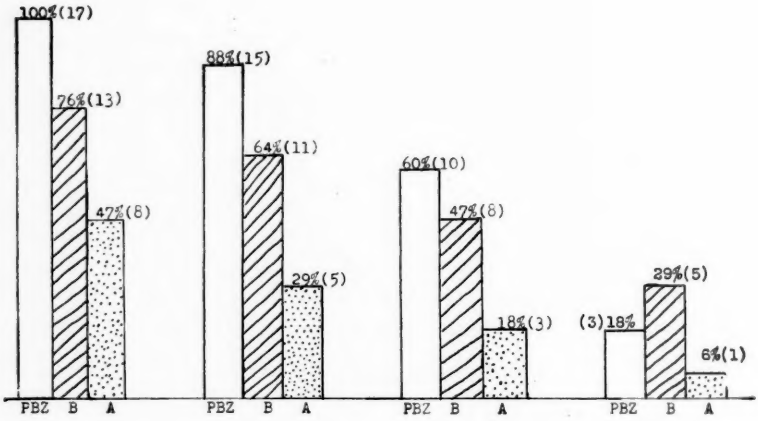

Fig. 1. Percentage somewhat relieved.
Fig. 2. Percentage satisfactorily relieved.
Fig. 3. Percentage showing side effects.
Fig. 4. Percentage showing objectionable side effects.

The result of the substitution of Antistine for Benadryl or Pyribenzamine in these seventeen patients is as follows: Only eight obtained some relief with Antistine. Nine experienced no relief. Of the eight benefited, five termed the relief "good," but only three thought Antistine better than Pyribenzamine or Benadryl—No. 1 and No. 14, both children, and No. 7, a woman. Of all seventeen taking Antistine, only three had side effects: mild nausea and listlessness in two, and nausea and vomiting in one, the latter the only one of the entire trial group to find Antistine objectionable.

On a percentage basis (Figs. 1 and 2), Pyribenzamine gave some relief to 100 per cent of this small highly sensitive ragweed pollenosis group; Benadryl gave some relief in 76 per cent, and Antistine in 47 per cent. However, relief enough to be called "satisfactory" occurred in 88 per cent with Pyribenzamine, in 64 per cent with Benadryl, and in only 29 per cent with Antistine.

As to side effects, some occurred in 60 per cent with Pyribenzamine, in 47 per cent with Benadryl, and in 18 per cent with Antistine. These side effects were severe enough to be objectionable in 18 per cent with Pyribenzamine, in 29 per cent with Benadryl, but in only 6 per cent with Antistine.

It is interesting to note that the percentage of satisfactory relief obtained with Pyribenzamine and Benadryl in this small group corresponds well

with the percentages reported in the literature.[1,2,4,7] As far as Antistine is concerned, the percentage figures on relief obtained, and on severe side reactions, almost parallel the figures reported by Chobot in the recent "Report of the Committee on Therapy of the American Academy of Allergy."[3]

Since no distinction was made between adults and children as to dosage, children received relatively larger amounts of the drug than adults. Perhaps this explains why the only patients receiving satisfactory relief from Antistine were two children, aged three and three and a half, respectively, and one woman whose reactivity to all drugs was extremely high. It may be noted that none of the children in the group had unpleasant side effects from Antistine in spite of the relatively higher dosage.

CONCLUSIONS

1. Antistine, in 100 to 200 mg. doses, proved much less effective than 25 to 50 mg. doses of Pyribenzamine or Benadryl in the relief of seventeen specially selected, highly sensitive, ragweed hay fever patients during the height of the ragweed season.

2. There are some indications that, due to its relative lack of side effects and to the relatively higher dosages tolerated, Antistine may be of special value in the treatment of allergic conditions of children, and also of adults highly reactive to drugs.

201 Dryden Bldg.

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BENADRYL: INTRAVENOUS USE IN ALLERGY

BENJAMIN ZOLOV, M.D., F.A.C.A.
Portland, Maine

THE purpose of this preliminary report, which involves the use of Benadryl intravenously in twenty-six patients, is to describe the method of administration and the results observed. The drug was given to twenty-three patients in the office and to three in the hospital. In all cases, the Benadryl, 10 mg./c.c. was diluted in 2 c.c. of normal saline and given intravenously with a 22-gauge needle over a period of two minutes. Each patient was observed for one-half hour to observe any immediate effects. Some patients received the drug on several occasions, the dose being increased from 10 to 20 mg., with similar results observed with the larger dose. One hospital patient received 30 mg. of Benadryl in 100 c.c. of normal saline, by the drip method over a ten-minute period, on six occasions.

Several recent reports have been made on the use of Benadryl given intravenously. An acute attack of bronchial asthma in one patient was completely controlled by the administration of 8 mg. of Benadryl intravenously in five minutes, according to a report of Cohen et al,[3] who also observed that the histamine threshold in this patient, as measured by the wheal and flare response forty-five minutes after giving Benadryl, was 1:200,000 as compared with 1:6,400,000 before treatment.

In the course of treating patients for ivy poisoning, Blumenthal and Rosenberg[1] found they could readily determine whether or not a patient would respond to Benadryl by testing its antipruritic effect when given intravenously. Thirty mg. of Benadryl were diluted with 100 c.c. of normal saline solution and administered intravenously over a period of ten minutes. If relief of symptoms was noted at the end of this time, the patient could reasonably be expected to respond to peroral Benadryl. Blumenthal and Rosenberg[2] also report the use of Benadryl intravenously in the prevention of transfusion reactions. They concluded that several of their patients appeared to benefit from the use of this drug with doses of 20 to 50 mg. in 100 c.c. of normal saline, given intravenously in a ten-minute period. Ten of eleven patients with urticaria had complete cessation of itching at the end of the injection. This relief from the pruritus lasted four to eight hours. The itching in two cases of contact dermatitis was controlled, while two cases of bronchial asthma were not helped by the above method. McGavack et al[4] reported dramatic relief in migraine following an intravenous injection of 20 mg. of Benadryl.

DISCUSSION

In the series of cases being reported, there were fourteen females and twelve males; the youngest was seven and the oldest seventy-three years of age. There was no essential change in the blood pressure before and after

TABLE I

Patients	Sex	Age	Diagnosis	Benadryl I.V.	Results		
					No Relief	Improved	Excellent
1. M. C.	F	43	Bronchial Asthma	10 mg. & 15 mg.		x	
2. I. D.	M	50	Bronchial Asthma	10 mg.		x	
3. P. C.	M	47	Bronchial Asthma	10 mg.	x		
4. R. D.	M	23	Bronchial Asthma	15 mg.	x		
5. J. H.	M	17	Bronchial Asthma	10 mg.	x		
6. K. H.	F	37	Bronchial Asthma	15 mg.		x	
7. G. C.	M	55	Bronchial Asthma	10 mg.	x		
8. C. S.	F	56	Bronchial Asthma	10 mg.			x
9. G. M.	M	50	Bronchial Asthma	15 mg.		x	
10. B. C.	M	50	Bronchial Asthma	15 mg.	x		
11. B. V.	F	21	Bronchial Asthma	25 mg.		x	
12. J. H.	M	42	Bronchial Asthma	15 mg.			x
13. R. T.	M	7	Bronchial Asthma	10 mg.	x		
14. E. D.	F	59	Bronchial Asthma Constitutional Reaction	10 mg.			x
15. E. H.	F	63	Ragweed Hayfever	10 mg.			x
16. K. H.	F	37	Ragweed Hayfever	15 mg.		x	
17. C. S.	F	56	Ragweed Hayfever	10 mg.			x
18. B. G.	F	30	Ragweed Hayfever (6 mo. Pregnancy)	10 mg.	x		
19. C. R.	F	35	Poison Ivy	10 mg.			x
20. C. E.	M	30	Neurodermatitis	10 mg.	x		
21. G. C.	M	55	Neurodermatitis	15 mg. & 20 mg. (twice daily) (chills on one occasion)			x
22. T. B.	F	40	Vasomotor Rhinitis	15 mg. & 20 mg. (severe headache 12 hrs.)		x	
23. S. K.	M	57	Vasomotor Rhinitis	10 mg.		x	
24. J. B.	F	73	Vasomotor Rhinitis	10 mg.	x		
25. S. A.	F	42	Angioneurotic Edema	10 mg.		x (3 hrs.)	
26. P. R.	F	50	Dermatitis Medicamentosa Uremia	30 mg.		x	

the injections. Complete blood counts were carried out with the hospitalized patients, and no abnormalities were observed. No sedative effect was seen in the office patients. Surprisingly enough, but doubtless due to the small doses used, only one patient complained of any nausea. This hospitalized patient, suffering with bronchial asthma, complained of nausea immediately after 15 mg. had been injected, although relief was obtained.

A forty-year-old woman with vasomotor rhinitis complained of an intense headache which started one hour after the injection of 20 mg. of Benadryl, and which persisted for twelve hours. Aspirin gave no relief. Another hospital patient complained of moderate chills, lasting thirty minutes, beginning one hour after injection. There was no further recurrence of symptoms with subsequent doses.

Those patients suffering with acute bronchial asthma and hay fever obtained relief from intravenous Benadryl in five to fifteen minutes. They remained free of symptoms for approximately three to four hours. The pruritus from poison ivy was relieved for six hours by this method.

REPORT OF CASES

Case 1.—A fifty-five-year-old man was admitted to the Portland City Hospital in August, 1947, with severe neurodermatitis of two months' duration involving his face, neck, arms and legs. The itching and discomfort were intense. No oral medication had been used for ten days. Local treatment consisted of the applica-

TABLE II. BENADRYL INTRAVENOUSLY

Condition	Number Treated	No Improvement	Improved	Excellent
1. Bronchial Asthma	14	6	5	3
2. Poison Ivy	1			1
3. Hay Fever (Ragweed)	4	1	1	2
4. Vasomotor Rhinitis	3	1	2	
5. Angioneurotic Edema	1		1	
6. Neurodermatitis	2	1		1
7. Dermatitis Medicamentosa Uremia	1		1	
Totals	26	9	10	7

tion of cod liver oil ointment. Benadryl (15 mg.) was administered intravenously twice daily at eight-hour intervals. The patient was thus completely relieved of the pruritus. At the end of a ten-day period, 50 mg. of Benadryl were given orally four times daily, with control of all symptoms. The skin lesions healed well by the end of three weeks.

Case 2.—A forty-year-old woman developed angioneurotic edema after using Sulfacetemide over a ten-day period for a mild conjunctivitis. She was given 10 to 20 mg. of Benadryl intravenously on four different occasions. Her symptoms were controlled only for a period of three hours.

Case 3.—A fifty-year-old woman was admitted to the Maine General Hospital in September, 1947. She had had bronchial asthma for many years. Surgical removal of a malignant rectosigmoid carcinoma, with a colostomy, had been performed one year previous to admission. Her blood urea was 160 mg. on admission. One week later it had decreased to 90 mg. She developed a generalized severe diffuse maculopapular rash, confluent over the shoulders, arms and legs, and associated with severe restlessness. She had received morphine and Pantapon immediately prior to the appearance of her rash. She scratched the lesions constantly and vomited almost daily from this time until her death three weeks later. Intravenous Benadryl was given on six occasions, in doses of 30 mg. in 100 c.c. of normal saline over a ten-minute period. These injections enabled her to have periods of rest, with the pruritus subsiding and with the skin lesions healing slightly. The patient's condition continued to deteriorate with progression of the uremia. A transfusion in reaction followed her first transfusion. Intravenous Benadryl, 30 mg. in 100 c.c. of normal saline, given several hours before two subsequent transfusions, apparently prevented reactions to these transfusions. Autopsy demonstrated markedly dilated ureters as a result of adhesions and metastases posterior to the bladder region, which constricted the ureters.

Case 4.—A patient who had an attack of bronchial asthma following pollen injection was given 0.5 c.c. of epinephrine 1:1,000 at fifteen-minute intervals without any relief. Intravenous Benadryl (10 mg.) was given at the end of three-quarters of an hour with prompt relief in fifteen minutes.

SUMMARY

A total of twenty-six cases were treated with small doses of intravenous Benadryl: fourteen with bronchial asthma, one with poison ivy, four with hay fever (ragweed pollenosis), two with neurodermatitis, one with angioneurotic edema, three with vasomotor rhinitis, and one with dermatitis medicamentosa and uremia.

Nine patients showed no improvement. Ten were improved, and excellent results were obtained in seven cases. The use of the drug was not consistently effective in any one of the patients treated. Caution was required since the drug was administered to ambulatory office patients. With those patients unable to tolerate oral medication, the method offers excellent relief by parenteral administration.

The number of side reactions observed was small. Further study of the use of Benadryl intravenously should serve to establish its proper use in allergy and allied conditions. Its administration in these patients subject to transfusion reactions, and also as prophylaxis in this field, should suggest further study.

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296 Congress Street

SENSITIVITY TO A SPECIFIC HUMAN DANDER

(Continued from Page 216)

SUMMARY

1. Dermatitis as a sole manifestation of the sensitivity to a specific human scalp dander is reported for the first time.

2. The specificity was to scalp dander alone; no sensitivity could be shown to either general body dander or stock human danders.

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5038 Jenkins Arcade Building

THE ROLE OF STREPTOCOCCI IN BRONCHIAL ASTHMA

(Continued from Page 249)

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ALLERGY AS THE CAUSE OF MULBERRY HYPERTROPHY OF THE INFERIOR TURBINATE

LINDEN J. WALLNER, M.D.
Chicago, Illinois

THIS is a report of a clinical and pathologic study of the effect of allergy in the production of mulberry degeneration of the posterior ends of the inferior turbinates.

This form of chronic hypertrophic rhinitis has been well described in the standard texts for years. There is a drawing of their appearance in Mackenzie's work[5] published in 1880, with a full description of the symptoms, pathology and method of removal through the nose with the snare. In drawings of the posterior rhinoscopic views of chronic sinusitis in Watson-Williams,[7] the inferior turbinates are pictured with these enlargements. Of the recent texts, Lederer[4] has a most complete description.

ETIOLOGY

In all the articles the etiology is given as a long-lasting chronic catarrhal rhinitis. Burnham[2] studied the cavernous tissue of the turbinates in detail. His explanation of this occurrence on the posterior free end of the turbinate is quite involved. Briefly, it is said to be due to a chronic stasis of the cavernous spaces of the anterior portion of the turbinate. Arnaud[1] says it is the result of any form of chronic rhinitis, including nasal hydrorrhea. Lederer[4] states it is due to a prolonged chronic simple or intumescent (vasomotor) rhinitis; he noted frequent occurrence of this condition in cases with mucous polyps. None of the articles mentioned allergy as the direct cause. Nasal allergy is now being diagnosed much more frequently, and many clinicians assume these mulberry ends to be indicative of allergy. No published reports of the proof of this relationship have been found in the literature.

SYMPTOMS

The two main complaints caused by these enlargements are nasal obstruction and postnasal discharge. These, of course, are two of the most common nasal complaints, and may occur as a result of a number of other conditions. The obstruction is located in the narrowest portion of the nasal airway, the choana, and may be severe. Some patients notice than they can inhale freely through the nose, but experience obstruction on expiration. This valve-like action can be explained by the fact that the mass is quite movable, having a somewhat pedunculated attachment in many instances.

From the Department of Otolaryngology, University of Illinois and Presbyterian Hospital, Chicago.
Candidate's Thesis, Chicago Laryngological and Otological Society.

DIAGNOSIS

These hypertrophies may be easily overlooked on routine examination. They must be searched for by posterior rhinoscopy, either with the mirror or the electric nasopharyngoscope. The mirror seems more simple for routine use, and gives a better view of the entire field. In the exceptional

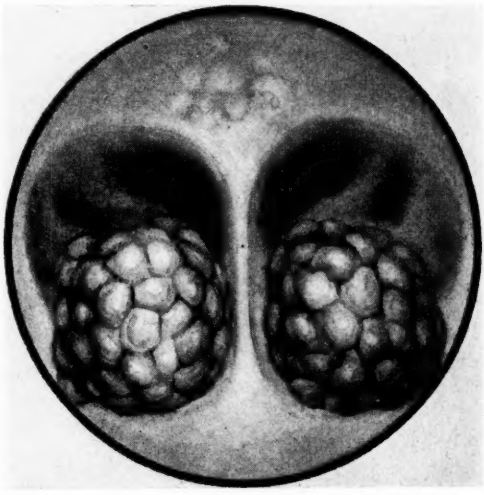

Fig. 1. Drawing of mirror view of mulberry degeneration of the inferior turbinates.

case, such as in exaggerated pharyngeal reflexes and in children, the nasopharyngoscope may serve to greater advantage. With either method it is important to visualize the choanae before an astringent is used. These enlargements do not disappear on shrinking, but there is enough reduction in size to prevent a true estimation of the resultant obstruction and to render their detection more difficult. There is considerable variation in the appearance of the posterior ends of the turbinates. They may appear quite bulbous, and purplish to blue in color. This is due to simple intumescence and disappears on the application of astringents. The mulberry ends have a pebbled effect. They often fill most of the choana, blocking a view of the middle, and even the superior turbinate (Fig. 1). After the mucosa of the nose has been shrunken with cocaine or ephedrine they may often be seen by anterior rhinoscopy. They may be lifted with a probe, revealing them to be quite movable due to their pedunculated attachment. The condition is usually bilateral, though one turbinal end may be considerably larger than the other.

It is almost always the posterior free tip of the turbinate that is involved. The anterior tip of the inferior turbinate may also be the site of origin. In one patient in the series, a twelve-year-old child, with severe allergic

rhinitis, the typical mulberry change occurred at the anterior end of the turbinate, completely blocking the nares.

The patients in this study were seen too recently to determine the

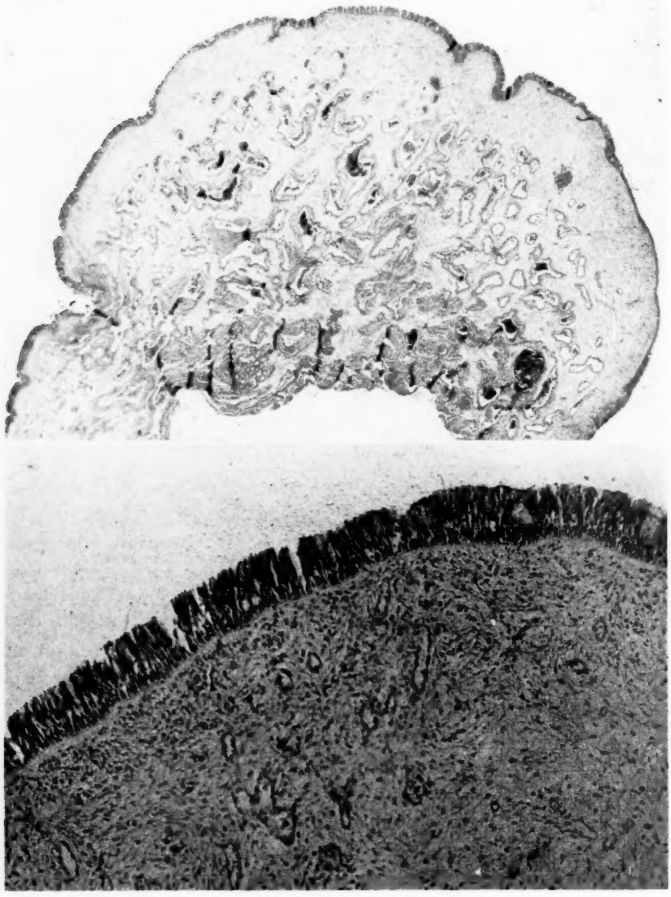

Fig. 2. *(above)* Photomicrograph, low power, of mulberry posterior end of inferior turbinate. Patient A.T., severe allergic rhinitis with mucous polyps.

Fig. 3. (*below*) Higher Magnification of specimen in Figure 2. Note papillary epithelium, thickened basement membrane, proliferation of fibrous tissue of the stroma.

likelihood of recurrence after removal. No mention of the return of these enlargements was found in the literature. Other patients in whom they have been removed have been followed for several years without evidence of recurrence.

CLINICAL AND PATHOLOGICAL STUDIES

This report is based upon the study of 106 cases. The attempt was made to determine whether these mulberry ends represent a specific

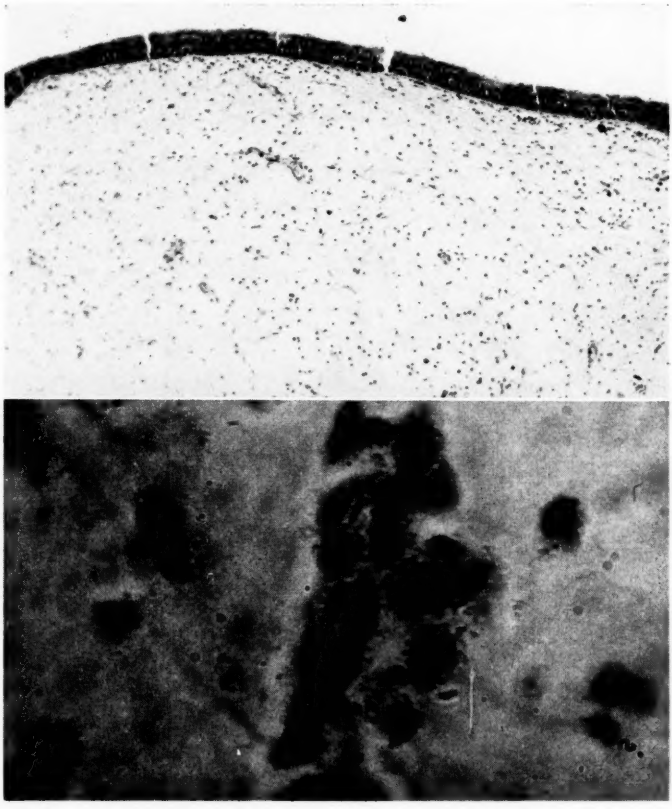

Fig. 4. (*above*) Section of a mucous polyp from Patient A.T. Note even epithelium, lack of basement membrane, loose stroma. The cells are mostly eosinophiles.

Fig. 5. (*below*) Photomicrograph of nasal smear from same patient, A.T., showing eosinophiles.

allergic change, such as is considered responsible in the majority of cases with mucous polyps.

The first group in the series consisted of patients with proven nasal allergy. Included were those with seasonal and perennial rhinitis, nasal polyps, and chronic hyperplastic sinusitis. The diagnosis of allergy was made by the history, the appearance of the nasal mucosa, nasal smears for eosinophils and, in some instances, by confirmatory skin tests. These patients were examined for the presence of these mulberry ends.

The second group comprised patients in whom these hypertrophies were

discovered on a routine nose and throat examination. They were studied for the presence of nasal allergy by means of the history, appearance of the nasal mucosa, nasal smears, and skin tests.

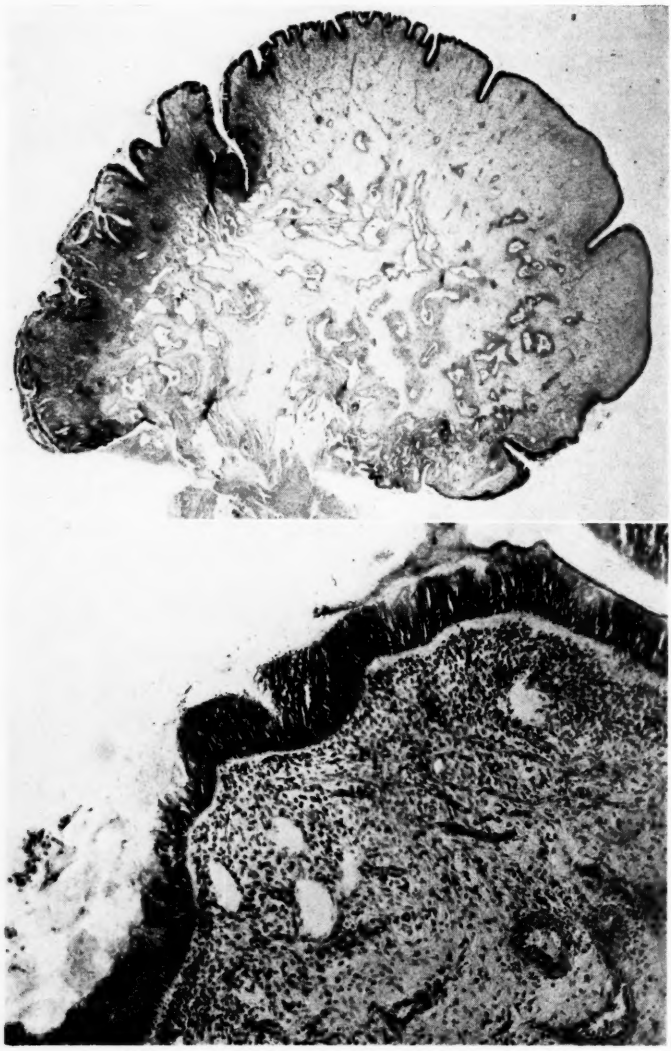

Fig. 6. (*above*) Photomicrograph, low power, of typical mulberry formation of the inferior turbinate. From a patient, Mrs. O., sixty-eight years of age. Has had a complete unrepaired cleft palate. No evidence of allergy discovered, etiology would seem to be the long continued exposure of nasal structures to unnatural trauma of the mouth. Note similarity to Figure 2.

Fig. 7. (*below*) Higher magnification of tissue in Figure 6. Patient Mrs. O. Compare with Figure 3.

All the enlargements that were removed were sectioned for histologic study. If mucous polyps were also present, one was studied for comparison. Sections of this region of the turbinate were also taken from stillborn infants at autopsy, and from the apparently healthy noses of adults, for a comparison of the normal histology of a control group.

RESULTS

Of seventy-five patients with definite nasal allergy, the typical mulberry enlargements were found in forty-five. Of fifty-eight individuals with polyps and perennial allergic rhinitis, in whom symptoms were present the year round, thirty-seven were found to have mulberry changes. Of seventeen persons with seasonal hay fever, with little or no symptoms at other times, only five were found to have these mulberry ends.

In the second group, twenty-four patients with mulberry enlargement were found on routine nose and throat examination. In twelve of these the presence of nasal allergy could be demonstrated from the history, the appearance of the nasal mucosa, nasal smears, or from skin tests. There is no simple method to rule out allergy. It is therefore possible that more than twelve had some allergy that was not apparent. In the twelve that were considered to be not of allergic origin, the diagnosis of chronic intumescent or vasomotor rhinitis was made.

PATHOLOGIC FINDINGS

Gross.—The attachment is somewhat pedunculated, one-half to one-third the size of the entire enlargement. The cut surface of this attachment is quite dense and firm, and blood vessels and cavernous spaces may be seen. These enlargements are usually round, and the color varies from red to purplish to quite pale. The surface is covered with papillary irregularities, making the term "mulberry" most appropriate.

Microscopic.—Sections were studied for changes in the epithelium, the basement membrane, the type and degree of cellular infiltration in the lamina propria, the number and activity of the glands, the blood vessels and the stroma.

Epithelium.—All sections revealed the epithelium in papillary folds, and many layers thick. In some regions it was composed entirely of goblet cells. Compared to the even columnar epithelium of the newborn these changes were quite marked. When compared with sections from adult "normal" noses, the changes were less conspicuous.

Basement Membrane.—Some of the most marked changes were seen in this region. It was found to be quite thickened in all hypertrophies as well as in the adult controls. None was observed in the newborn. Con-

siderable variation in different regions of the same section was evident. No significant difference could be noted between the allergic cases and those diagnosed as intumescent (vasomotor) rhinitis.

Cellular Infiltration.—There was wide variation in the degree of cellular infiltration in different sections, as well as in different regions of the same one. The cells were mostly of the small, round cell type. Plasma cells were numerous. The small number of eosinophils found in the allergic patients was surprising, when compared with the nasal smear and a section of a polyp from the same patient.

The stroma was loose and edematous in the allergic patients. This edema was located mainly in the subepithelial region. The deeper layers of the lamina propria were made up of more dense fibrous tissue, especially surrounding the venous spaces.

The pathologic findings in mulberry enlargement of the inferior turbinate may be summarized thus: There is hypertrophy or actual increase in size, due to proliferation or hyperplasia of the connective tissue elements of the stroma, covered with a papillary type of epithelium.

DISCUSSION

From the clinical examination, it appears that these mulberry ends are associated with nasal allergy in a high percentage of cases, great enough to suggest cause and effect. They were found more often than nasal polyps in the group of allergic individuals. The changes seen in a study of sections of the hypertrophies removed is not compatible with allergy. Hansel[3] says that the typical changes of allergy are edema and eosinophilic infiltration. He describes thickening of the basement membrane but does not believe it to be a specific change of allergy. Shambaugh[6] studied the basement membrane in sinus disease. He found that 75 per cent of patients with asthma revealed thickening of the basement membrane of the sinus mucosa. He did not conclude that it was significant of allergy. Hansel[3] describes the papillary changes of the mucosa as due to newly formed fibrous tissue, and he believes this is a change indicative of infection, not allergy. It is particularly this papillary change, with hyperplasia of the stroma, that was characteristic of the changes observed in these enlargements. No marked differences could be made out between those persons diagnosed as allergic and those of chronic intumescent rhinitis. In discussing this increase in fibrous tissue, Lederer[4] states that it is due to the increased blood supply of a chronically congested turbinate. Allergic rhinitis has a chronic hyperemia and engorgement of the venous spaces as well as edema. The disease other than allergy found in these patients with mulberry enlargement was chronic intumescent rhinitis, a condition characterized by chronic engorgement of the cavernous spaces. It would seem that this venous stasis is the best explanation of the production of mulberry hypertrophies. While they occur so frequently in allergic

rhinitis, they are not a result of allergy *per se* but of the continuous intumescence of the turbinate that accompanies it. They occur often enough in allergy that their presence should suggest an underlying nasal allergy.

SUMMARY AND CONCLUSIONS

1. Mulberry enlargement of the posterior end of the inferior turbinate is a common cause of nasal obstruction and postnasal discharge.

2. These hypertrophies are best seen by posterior rhinoscopy. This should be a part of any routine examination of the nose.

3. In a group of seventy-five patients with definite nasal allergy, mulberry enlargements were found in forty-five. In another group of twenty-four in which these enlargements were discovered on routine nose examination, the presence of nasal allergy could be shown in twelve.

4. In fifteen patients these hypertrophies were removed and studied, and compared with sections of the posterior tip of newborns and adults with no apparent enlargements. The most significant changes observed were papillary hypertrophy of the epithelium and hyperplasia of the connective tissue elements of the stroma, alterations considered to be due to inflammation rather than to allergy. With the exception of eosinophilic infiltration, no differences were seen in the hypertrophies taken from allergic patients and those in whom no allergy was demonstrated.

5. The production of these hypertrophies is best explained as due to a continuous venous stasis. They are most frequent in patients with nasal allergy, but other conditions such as intumescent (vasomotor) rhinitis are also capable of producing them.

6. The presence of these enlargements is a nonreversible change. They cannot be caused to disappear by allergic management alone. When large enough to cause obstruction, they should be removed by means of a snare.

122 South Michigan Avenue

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

ALLERGY OF THE PANCREAS AND OF THE SALIVARY GLANDS

It is a well-known fact that allergic involvement may occur in any part of the alimentary tract. Although allergy of the salivary glands has been known for some time, it is not generally appreciated and is frequently not recognized.

There remains one organ in the alimentary tract, however, the allergic involvement of which has not been reported until recently, and that is the pancreas. In a recent issue of the *Permanente Foundation Medical Bulletin,* a case of allergic pancreatitis was reported by Shaffer. A review of the literature revealed no previous report of a similar case.

Shaffer's patient was that of a man, aged forty-eight, who entered the hospital with the complaint of hives and abdominal pain of twenty-four hours' duration. After the onset, the hives became generalized and increased in severity. Ten hours before the onset of the hives, he suffered constant, severe, sharp cramping pain in the midepigastrium radiating to the back. The pain was associated with nausea and vomiting, but no diarrhea. The injection of 1 c.c. of epinephrine somewhat relieved the hives, but not the abdominal pain.

The patient had had almost continuous urticaria since 1942. On two occasions during the past year, severe abdominal pain occurred with generalized urticaria. One attack was relieved by epinephrine, the other by intravenous procaine.

In 1943, the patient was operated upon for acute pancreatitis. Urticaria was present at that time. At operation, pancreatitis was noted and the biliary tract drained.

When the patient was first observed by Shaffer on June 3, 1947, he had giant urticaria with swelling of the eyelids and tongue. There was diffuse abdominal tenderness, with muscle spasm, more pronounced in the midepigastrium. The blood count and routine urinalysis were not significant. Serum amylase was 300 units and urine amylase 438 units on June 3, 1947. On June 9, 1947, the serum amylase was 115 units and the urine amylase 140 units.

Upon admission to the hospital, the patient received 150 mg. Pyribenzamine and 100 mg. four times daily thereafter. Within three hours the pain was relieved and the urticaria had almost subsided. After four days the patient was symptom free.

In a review of the pertinent literature, Shaffer calls attention to the

report of Necheles et al on allergy of the gall bladder, in which it was stated that mucous plugs containing numerous eosinophiles were noted in the cystic duct at operation.

Shaffer also reports two additional cases of allergic pancreatitis observed by Stuart Lindsay. The pancreatitis developed after the ingestion of foods which had previously caused abdominal distress.

In the observations of patients with food allergy, especially those who have angioneurotic edema and urticaria, allergic involvement of the salivary glands and the pancreas must occur more frequently than generally realized. In 1940, we had occasion to observe a patient with recurring swellings of the parotid gland associated with attacks of generalized urticaria. A mucous plug expressed from Stenson's duct showed a very large number of eosinophiles, thus establishing the diagnosis of allergy of the parotid. Since that time, eight similar cases have been observed. In 1937, Rowe reported a case of allergy of the submaxillary gland. He referred to Pearson's report of seventeen cases of allergy of the parotid which appeared in 1935. Pearson injected lipiodol into the ducts and found that they were in a state of dilatation. Since the swelling of the gland usually subsides with the expression of the mucous plug from the duct, the involvement must be caused by duct obstruction rather than generalized edema of the gland. More recently, Waldbott and Shea reported three cases of parotid allergy in asthmatic patients.

In 1933, Londe and Pelz reported a case of recurrent parotid swelling associated with attacks of abdominal colic. With the recognition of allergy of the salivary glands, we suggested that a similar involvement of the pancreas was a possibility, but such a case has not come under our observation, although we have been on the lookout for its appearance.

These points on allergy of the pancreas and the salivary glands are presented with the idea of provoking more attention to the recognition and proper management of these cases when they make their appearance.

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Progress in Allergy

PEDIATRIC ALLERGY

A Critical Review of Recent Literature

JEROME GLASER, M.D., F.A.C.A.
Rochester, New York

BRONCHIAL ASTHMA

Buffum[16] has made a very excellent attempt to determine the characteristic features of asthma occurring during the first two years of life. From his observation and reports of others, it appears clear that one-fifth to one-third (20 to 33 per cent) of asthmatic children develop this disease before they are two years of age. Of the author's 265 cases, eighty-five or 32 per cent had their first attack before the age of two years. Of these eighty-five cases 32 per cent were classified as severe and of the 180 cases starting after the age of two years, 20 per cent were considered severe. This suggests that asthma beginning before the age of two years is more likely to be severe than that beginning later in childhood.

Skin tests were found of definite help in the planning of treatment. The infants usually had multiple sensitivities both to inhalants and foods. One infant was completely relieved by sulfadiazine and two others were completely relieved for long periods of time by treatment with intramuscular penicillin. This is assumed to be due to the effect of these drugs upon superimposed infection which may initiate or prolong attacks. There was no evidence that bacterial allergy was the sole cause of asthma in any case.

Eleven cases were reported in detail. Of thirty-eight patients treated for a period of one year, the results were perfect or almost perfect in thirteen (34 per cent); fair or poor in seventeen (45 per cent) and not known in five (13 per cent).

An important characteristic of asthma in infancy results in the fact that the diagnosis of bronchial asthma is not always made early. The wheezing, prolonged expiration and musical râles, which are typical of asthma in later life, are often absent in infancy. Instead there is a noisy breathing with only moderate dyspnea, and on auscultation only loud trachael râles are heard. This noisy breathing, which does not seem to be typical of anything, may lead one away from the diagnosis of asthma which ultimately is made on the basis of the history, skin tests, blood eosinophilia and the ruling out of other causes of dyspnea.

An interesting report on asthma in the newborn in Hawaii is presented by Nance.[53] Seven case reports are given to illustrate the following points: (1) asthma in the newborn is not uncommon but is probably the most frequent cause of a wheeze in these infants; (2) it is almost always dietary in origin; (3) since the diet at this age is extremely limited, the detection of the offending food is often a very simple matter.

The cases presented ranged in age when first seen because of asthma from two to ten months. In all instances wheezing had started at birth. The patients included one Chinese, one Japanese, one Korean, one Hawaiian, two Caucasions and one whose racial origin was not stated. In five of the seven cases "enlarged thymus" had been erroneously diagnosed as the cause of the wheezing. In six patients the asthma was due to cow's milk and in one case to breast milk. Six patients did well on evaporated goat's milk; one on Nutramigen.

From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry and the Pediatric Services of the Strong Memorial, Municipal and Genesee Hospitals, Rochester, New York.

The history that an infant has "wheezed since birth" plus the presence of an expiratory wheeze should suggest a probable diagnosis of asthma due to food allergy. The diagnosis of enlarged thymus must be received with skepticism.

(The reviewer notes that allergic bronchial asthma is ordinarily not a difficult diagnosis to make but it is in infancy and childhood that most problems of differential diagnosis arise. Dyspnea due to enlarged thymus or other intrathoracic tumor though rare does occur and must be considered. The reviewer is also unwilling to accept breast milk as the cause of asthma in the case mentioned as there is no statement of any attempt to control the mother's diet as regards foods, such as egg, for example, which could be excreted in the breast milk and cause allergic manifestations in the infant. So far as the reviewer has been able to discover, there is, in the literature, no authentic, fully controlled report of allergy to breast milk in a human infant.)

The problem of food as related to older asthmatic children has been further studied by Hill.[40] One hundred children three to twelve years of age were observed. Thirty-five gave one or more positive tests to foods; sixty-five gave none. There was no reason to believe that asthma was caused by food in any of those who gave negative tests. Routine intracutaneous tests to foods are no longer done in Hill's clinic because so many positive reactions were obtained which had no clinical significance that helpful information very rarely resulted. This is not the case, however, with environmental allergens when the scratch tests are negative. These intradermal tests when positive usually indicate clinical sensitivity. In twenty-four of the 100 children studied asthmatic attacks had been or could be produced by the ingestion of a specific food. In most cases, also, the parents knew which foods produced the symptoms.

In the 100 children there were 218 positive scratch tests to foods. Of these there were forty-four in which it was definitely proved that the food in question could cause asthma. Thus about a fifth of the positive scratch tests to foods in asthmatic children were of etiological significance. Eggwhite, fish, peanut, walnut and chocolate accounted for thirty-eight of the forty-four etiologic tests. In sixteen cases (8 per cent) a food that gave a positive scratch test caused irritation about the mouth, vomiting, urticaria or angioneurotic edema but no asthma. The author's figures agree with those of other investigators. Wheat and milk, which may be of considerable importance in atopic dermatitis in infants and in many other allergic conditions, rarely caused asthma in the children studied, and positive scratch tests to these substances were not common. Some of the positive skin reactions were to foods which were of etiological significance when the child was younger but although the positive skin test persisted, clinical sensitivity had been lost. While tolerance to foods is commonly eventually acquired as the child grows older, tolerance to environmental allergens occurs much less readily and sensitivity may persist throughout life.

Chobot[17] states that the importance of food sensitization in the early years cannot be overestimated. Together with bacterial allergy it comprises the entire cause of asthma in the first few years of life. Seventy per cent of children who had their first attack of asthma in the first three years of life had food as the basic etiologic factor.

(While granting the importance of food allergy and infection as important causes of asthma in infancy and childhood, the reviewer believes that it is exceedingly important not to neglect inhalant allergens which in his experience are at least of equal importance.)

Logan[47] lists the following conditions which have been mistaken for asthma at times: "rattle" in the throat due to excessive saliva or mucus; acute laryngotracheobronchitis; foreign body in the tracheal tree; bronchiectasis; lymphadenopathy,

most commonly at the bifurcation of the trachea; pulmonary manifestations of cystic fibrosis of the pancreas; relaxed larynx; mediastinal tumor, including Hodgkin's disease; retropharyngeal abscess; pertussis; dust bronchitis; and sighing dyspnea. The most common complications of asthma are atelectasis and emphysema. Bronchostenosis[62] may occur. This is a definite localized structural narrowing of a bronchus. The symptoms of this consist of a persistent dry cough, sometimes paroxyzmal, and high fever. The temperature usually falls rather abruptly to normal within a few days, immediately following which the cough becomes productive of a purulent and somewhat bloodstained sputum.

Logan[47] emphasizes the importance of history in the diagnosis and treatment of bronchial asthma. In the Mayo Clinic direct scratch testing is used in children up to the age of five years. If thought necessary, a few selected intradermal tests are done. In testing older children the intradermal method is used except for the food allergens. Intradermal testing in some instances should be preceded by scratch tests. (The reviewer feels that fewer mistakes would be made and much less harm would be done our patients if intradermal tests are in all instances preceded by scratch tests. This point has been repeatedly emphasized by Unger.[79]) Skin reactivity does not necessarily parallel the severity of the allergic disease. The author approves of Tuft's[78] suggestion that positive reactions should be repeated to be sure that they are really positive. (The reviewer feels that this suggestion of Tuft's is of the utmost importance. It is amazing to see how many positive tests may be obtained, even by the scratch method, particularly to foods, which cannot be repeated even when the testing is done at the same sitting.)

Anglade[2] studied the ability of 193 normal children from six to fourteen years of age to hold their breath and compared the figures obtained with those of asthmatic children. He found that the ability to hold the breath is decreased in proportion to the duration and severity of the asthma. The longer the child can hold his breath the better is the prognosis.

Lapage[43] of Manchester, England, has written a review of modern methods of treatment and prophylaxis of asthma in children. This review, which does not lend itself readily to abstracting, is very interesting chiefly because of the differences in viewpoints between the author and most American pediatric allergists. Symptomatic treatment and psychosomatic factors are emphasized and the search for specific factors receives little attention. Improvement resulting from change in environment is considered to be due largely to psychogenetic factors rather than escape from environmental factors.

TREATMENT OF BRONCHIAL ASTHMA

Logan[47] notes the particular value of the iodides in liquefying bronchial secretions and states that small doses may be ineffective. He gives 5 grains (0.3 grams) to most three-year-olds and 25 to 30 grains (1.6 to 2.0 grams) three times a day to eight-year-olds. He uses the saturated solution of potassium iodide or sodium iodide and gives this in fruit juice or syrup of honey. The use of syrup of ipecac in teaspoonful doses, which may be repeated in one-half hour if necessary, to loosen mucous plugs in asthma is mentioned. In the administration of epinephrine doses of more than 0.5 c.c. to a child are rarely necessary. If this is done, then the dose should be divided into several sites so that local vasoconstriction will not interfere with absorption. A serious misprint occurs in one of the tables in this article in which the subcutaneous injection of 1:100 aqueous solution of epinephrine is recommended. This should read 1:1000.

Ether and olive oil rectally (3 to 4 ounces in equal parts) may break up an attack of status asthmaticus. Bronchoscopy is occasionally necessary. The use of opiates is warned against but barbiturates or demerol are occasionally helpful. It is

exceedingly important to keep up the fluids in asthma; 1000 c.c. may be administered intravenously to children over four years of age if given slowly. Intravenous glucose is also of value. Hypertonic glucose is, however, dehydrating.

Chobot[17] states that status asthmaticus in a child differs in one respect from that in the adult in that it is usually of much shorter duration, lasting as a rule only two or three days in contrast to its duration in the adult where it may persist for weeks. The first step in the relief of this condition is to evacuate the bowels by the use of enemas and follow this by saline catharsis to take pressure off the diaphragm. (The reviewer notes that one of the most serious mistakes made in the treatment of status asthmaticus both in pediatrics and in internal medicine is the failure to keep up the patient's fluids. This results in drying and thickening of the secretions.)

Chobot comments that infections of the upper part of the respiratory tract are the most common causes of asthma in children. He advises early and complete removal of infected tonsils and adenoids. Autogenous vaccines are preferred to stock vaccines for treatment. (The reviewer, in common with most other pediatric allergists, finds that removal of the tonsils and adenoids does little or no good in bronchial asthma unless these are definitely infected. In the present light of our knowledge indications for the removal of the tonsils and adenoids in allergic children appear to be the same as in non-allergic children.)

The use of the roentgen ray for the treatment of lymphadenoid tissue in the nasopharynx, particularly in asthma, has been discussed in previous reviews, 1947 and 1948.[31] Hawley[39] reports twenty-eight patients, mostly children, treated by this method and followed for two years. The treatments were given principally for Eustachian tube obstruction, and were successful in removing the lymphoid tissue in every case. No significantly unfavorable reactions were noted. A few patients reported a slight dryness of the nasopharynx. One interesting subjective phenomenon was reported by an intelligent boy of eleven. He claimed that during the irradiation he detected an unidentifiable odor, neither pleasant nor unpleasant. Efforts were made to convince him that this was imaginary but without success.

Anrep and associates[3] have reported on the use of an extract, Khellin, of the seeds of Ammi visnaga (Arabic khella), an umbelliferous plant growing wild in the eastern Mediterranean regions which has been used by the local population since ancient times as an antispasmodic in renal colic and ureteral spasm. The active principle is a di-methoxy-methyl-firano-chrome and thus belongs to the same group as coumarines and possibly flavones. It causes a conspicuous and prolonged relaxation of all the visceral smooth muscle—the intestines, uterus, bile ducts, bronchi and especially ureters. It appears to be useful in angina and in bronchial asthma. The authors state that in the latter disease they treated forty-five patients (age not stated), forty-one of whom obtained complete and prolonged relief after one injection. In the doses recommended it is not toxic and the only fairly constant effect was a general sensation of warmth without actual flushing.

Segal and his associates* have, unfortunately, not found Khellin effective for the relief of bronchospasm when administered either orally or intramuscularly in asthmatic subjects. It was proved to be an ineffective antihistaminic and anticholinergic agent as determined by their protective studies in asthmatic subjects with experimentally induced broncospasm and dyspnea.

Pedrera[55] found excessive nervous reactions on the part of the mothers when he injected adrenalin in oil in children. He now uses the aqueous solution of adrenalin in doses of 2 to 3 minims as necessary.

Goldman[35] at the National Home for Jewish Children in Denver fed amino acids

*Personal communication to the author.

in the form of Hydramin (Nion Co.) to twenty-one asthmatic children, seven boys and fourteen girls. A group of sixteen girls and thirty-two boys was used as a control. One-half ounce of dry powdered Hydramin was given in a variety of vehicles to the members of the first group after each meal. The average age of the test group was 9.64 years; of the control group 10.60 years. The preparation was difficult to administer because of taste but on the whole it was taken regularly. After a twelve-week period the average gain in the control group was 1.12 lbs.; in the test group 2.59 lbs.; the control group gained 0.39 in. in height and the test group 0.52 in. While this series is small the results are encouraging and further experimentation along this line is indicated.

Wasson[81] continues to report good results in the treatment of asthma by ethylene disulphonate, unfortunately uncorroborated by other investigators with the exception of Bartlett.[10]

ANTIHISTAMINICS IN BRONCHIAL ASTHMA

It is the experience of most allergists that the antihistaminics are of very little value in bronchial asthma. When relief is obtained, particularly in infants and children, it is often exceedingly difficult to determine whether this is due to the antihistaminic or the sedative action of these drugs. That these drugs are in some individuals very efficient and powerful hypnotics is becoming more and more evident as patients who discover this in using these drugs for the treatment of allergic conditions continue to use them even after the allergic condition has disappeared, for these sedative and hypnotic effects.

Logan's[47] results with Benadryl and Pyribenzamine in the treatment of asthma are far better than those reported by most. He attributes this to the use of drugs early in an attack. There is no doubt but that the earlier they are given, like the use of any other drug in the treatment of asthma, the more efficient they are.

Waldbott[80] has described a seven-month-old infant who had extremely severe attacks of asthma of unknown etiology recurring every ten days. The attacks lasted about ten to fifteen hours and always terminated in pneumonitis. During the course of the attacks extreme shock was present; the child was completely unconscious with marked cyanosis. The respiratory rate ranged between 80 and 90 per minute and the pulse rate could not be determined. Many unsuccessful efforts had been made to relieve the attacks. Following the oral administration of 50 mg. of Benadryl the child improved remarkably within one-half hour, the pulse rate dropping to 90 and the respirations to 36, and the episode considerably shortened. These observations were repeated on two successive occasions.

(The reviewer notes that there is no question concerning the occasional relief of asthma by antihistaminics but this is by no means constant or dependable. The reviewer has a physician friend, also an infrequent patient now and then who appear to get satisfactory relief from mild asthmatic attacks, independent of the sedative effects, by the use of Benadryl or Pyribenzamine. He has, however, never seen relief from severe bronchial asthma or status asthmaticus following the use of antihistaminics and while these drugs may reasonably be given a brief trial in these conditions, if relief is not immediate they should not be continued because of their tendency to dry and thicken the secretions.)

Bowen[13] has again brought up to date his comprehensive but concise views on the problem of the asthmatic child which were reviewed in 1948.[3] He states that there has not been a proven case of cottonseed oil sensitivity yet reported in the literature, nor has he seen a case of proven allergy to cane sugar. His experience with Nutramigen as a milk substitute has not been good. The administration of large doses of vitamin C to allergic patients is without benefit. Hypoimmunization against foods by injection is not without danger and as a routine measure is

to be condemned. Skin testing with foods gives less than 40 per cent reliable information. Food dislikes may occasionally be indicative of allergy but cannot be accepted as a true guide. Radiation treatment of recurrent or residual lymphadenoid tissue in the nasopharynx should be considered in the treatment of asthmatic children. Before treating asthma one should be sure that the diagnosis is correct. Environmental control is stressed. Allergic children should not have animal pets with fur or feathers. Occasionally a child following a hobby may be exposed to some unsuspected allergen, as glue in stamp collecting or the making of models. In skin testing scratch tests should be done first to insure safety and avoidance of systemic reactions. Intradermal tests may then be done in the case of scratches which reacted negatively. Bowen finds skin testing of little help in children under one year of age. An interesting speculation is that an apprehensive struggling child may produce enough epinephrine to interfere with the skin tests. The antihistaminic drugs are of little value in the treatment of asthma. Morphine should never be used in children, but demerol is permissible. Routine prophylaxis against pertussis, diphtheria, tetanus and smallpox should not be omitted. In the treatment of asthma with vaccine, stock preparations have proven as satisfactory as autogenous. The psychosomatic aspects of the management of the asthmatic child also deserve consideration. They should be encouraged to live lives as near like those of other children as possible.

BRONCHOPULMONARY AND UPPER RESPIRATORY DISEASES

Finke, in a series of four papers, has elaborated on his conception of bronchopulmonary disease, particularly as related to asthma. He emphasized[25] that, as discussed in the 1948 review,[31] common misinterpretation of symptoms and of associated conditions, which frequently disguise nontuberculous pulmonary infections, impede a prophylactic approach to chronic bronchitis and bronchiectasis. These diagnostic errors may delay adequate treatment in children who develop recurrent respiratory infections or persistent respiratory symptoms following measles, pneumonia or pertussis. Neither care of the tonsils, throat, or sinuses or allergic management of recurrent bronchitis, labeled "asthma," if infectious bronchitis produces asthmatic symptoms, forestall their chronicity. If penicillin areosol therapy is instituted early before irreversible changes have taken place, chronic bronchopulmonary disease may be prevented. Two hundred thousand to 400,000 units of penicillin are given daily for one or two weeks and continued with gradually decreasing doses for two to six months, in some cases longer, to assure definite arrest of the infection and prevent early relapse.

The importance of early correct diagnosis is emphasized and also that penicillin aerosol is topical therapy and so resulting blood levels are not important.

Finke emphasizes that it is not the fate of the individual patient alone that is at stake. Chronic pyogenic respiratory infection is, especially among the poor, a common falilial source of severe pulmonary affections in early childhood. It is responsible not only for the death of thousands of infants but also for the origin of chronic pulmonary infection in many more of those young children who survive. Unless such source of infection is eliminated, especially in afflicted veterans establishing their families after return to civilian life, the disease will claim new victims among the coming generations.

In another article Finke[26] stresses the production of asthmatic symptoms due solely to infection. He states that if one accepts an acute bronchopulmonary infection as the origin of infectious asthma, a rational therapy of this disease has to consider, most of all, its initial stage. The early elimination of the "focus of infection" in the lower respiratory system by all therapeutic measures at our command is the safest way to prevent its perpetuation regardless of the immunologic mechanisms pos-

sibly involved. (The reviewer notes that Finke gives the impression that the simultaneous occurrence of allergy and infectious asthma is mostly coincidental. This is hardly borne out by the fact that allergy had existed or was suspected in twenty-two of his 100 cases. A question to be solved in this problem is—if asthma symptomatically indistinguishable from that of allergic asthma may be caused by infection establishing thereby an entity called "infectious asthma," why are not all cases of bronchopulmonary infection accompanied by typical asthmatic breathing? There must be some underlying difference between the person who has a bronchopulmonary infection and wheezes and the person who has a bronchopulmonary infection without wheezing. In the present light of our knowledge, admittedly incomplete as it is, I believe the evidence is that it is the fundamentally or latently allergic individual who wheezes. An analogy to this is the opinion of Swineford and Magruder[76] to the effect that cardiac asthma occurs in basically allergic individuals with heart disease. The reviewer has previously pointed out[32] that asthmatic bronchitis is in all probability bronchitis occurring in an allergic or potentially allergic individual.)

Two simplifications of the use of penicillin aerosol for home treatment are discussed by Finke.[24] One consists of the use of an ordinary bicycle pump fastened to a board base. A filter containing glass wool is inserted into the hose leading from the pump to insure that the air passing into the nebulizer is cleansed of foreign matter. The medicinal end of the tube is fastened to the nebulizer. Very little effort is required by this method as compared to the tedious and tiresome process of compressing a hand bulb. Two sizes of pumps may be used—a larger size for adults and a smaller size which is easy for children to operate themselves. The use of triturate tablets of penicillin is also recommended as particularly convenient for home use because refrigeration is not required and manipulation of vials is not necessary. The pump may also be used in connection with head tents in the case of very young children. (The reviewer points out in this connection that it was Barach[9] who first used a bicycle pump to assist in the use of penicillin aerosol. Barach recommended a foot bicycle pump which many prefer to the hand pump.)

In the fourth publication[27] Finke discusses in detail the important subject of the prevention of chronic bronchitis and bronchiectasis in childhood. He points out that the common background of chronic bronchitis and bronchiectasis is usually chronic nontuberculous bronchopulmonary infection. Chronic bronchitis, with or without bronchiectasis, has its onset in such common childhood diseases as bronchopneumonia, pertussis and laryngotracheobronchitis. A common cause of the latter is exposure of children to chronic nonspecific pulmonary infections in the family. Of thirty-nine children over the age of two who had been hospitalized for acute bronchopneumonia, twenty-six had a definite history of recurrent respiratory episodes since infancy. Of fifty children hospitalized in 1945 for bronchopneumonia and treated with sulfonamides and/or penicillin, sixteen showed evidence of subacute bronchopulmonary infection two years later. Only ten had remained completely free from respiratory infections during the two years following their bronchopneumonia. Most children with chronic bronchopulmonary disease have had an adenotonsillectomy in an effort to alleviate this condition. The contrary result is more likely to be obtained and an attitude of conservatism is urged towards this operation.

As a method of therapy in the treatment of bronchopulmonary infection to prevent chronicity the use of penicillin aeosol is urged, 50,000 to 100,000 units two or three times a day for a week or longer. There appears to be no foundation for the fear that penicillin-fast organisms will develop and allergic reactions to penicillin rarely require discontinuance of the treatments. It is not important

to obtain significant blood levels since by this method of treatment the penicillin is used as topical therapy. A series of fifteen cases is tabulated.

(The reviewer notes that Finke's suggestions for the treatment of acute or subsiding bronchopulmonary disease in an effort to prevent chronic pulmonary pathology are highly logical and of great importance to the pediatrician. However, the author has completely neglected the fundamental basis of most recurrent respiratory disease in infancy and childhood, which is the allergic constitution. The fact that infection occurs as a result of edema in mucous membranes secondary to allergy is exceedingly important because by proper allergic management such infections may often be prevented. This fact, which is not mentioned by Finke, is fundamentally at least of equal importance to treating recurrent infections with penicillin aerosol because the latter therapy, important as it is, can be only palliative. It offers little for the prevention of future infections.)

Bronchiolitis, also called capillary bronchitis, is a disease of particular interest to the pediatric allergist because it resembles, at least superficially, bronchial asthma in many respects. It was reviewed in some detail in these columns in 1947.[31] It is apparently difficult or impossible at times to make a differential diagnosis between this disease and bronchopneumonia. Stiller[75] has recently reported a review of twenty-five consecutive cases. He points out that one of the chief characteristics of bronchiolitis is a generalized obstructive emphysema. This results in a roentgenogram which is typical of the disease. There is dyspnea of the expiratory type with exhaustion of the infant a prominent contributing cause of death. There is very often a continuous staccato hacking cough suggestive of pertussis. The most important cause is said to be the synergystic action of viruses and bacteria. Other causes are infection plus foreign body (amniotic fluid; vomitus; zinc stearate) and the interstitial pneumonitis of cystic fibrosis of the pancreas.

All twenty-five of the cases reported occurred in the early winter of 1946-47. Only one patient was over four months of age. Fever was relatively low, 76 per cent having temperatures under 103° F. The white count was normal or low in over half the cases with a relative lymphocytosis. Prolonged hacking cough was present in all cases. Cyanosis, substernal and diaphragmatic type retractions and asthmatic type breathing were present in many cases. All children looked acutely ill and most were considered in critical condition on admission. Roentgenograms showed generalized obstructive emphysema. Treatment was with penicillin and sulfadiazine. Oxygen was recommended for cyanosis; otherwise steam was used; occasionally both were used. There was but one death and no autopsy was obtained. The history of one case is given in detail.

The major diseases to be considered in the differential diagnosis are pertussis and asthma. Pertussis may be ruled out by culture. Asthma is rare under six months whereas 95 per cent of the cases of bronchiolitis occur before that age. Adrenalin and similar therapy was not found of value. Pratt,[61] whose work was reviewed[31] in 1947, states that aminophyllin is of great value in the treatment of this disease. Although he also states that there appears to be no evidence that allergy is a cause of this condition, this therapeutic measure is additional evidence of a possible relationship between bronchial asthma and this disease.

A case of Loeffler's disease in an infant, an exceedingly rare occurrence, is reported by O'Byrne.[54] This disease is characterized roentgenographically by a succession of transitory shadows which may appear in any part of the lung fields, be widespread and homogenous, spotty or cloudy, more or less sharply defined, may resemble tuberculosis or bronchopneumonia, and ordinarily do not remain in one spot for more than two weeks. As one shadow disappears, others may appear in different parts of the lung parenchyma. Serial roentgenograms are necessary for confirmation of diagnosis. Another characteristic is an eosinophilia which varies from 8 to 70 per cent. The disease is benign; the temperature rarely goes over 101° F. There may be slight

cough and pleurisy. The physical signs on auscultaton of the chest are usually negative. The condition may be due to a number of allergens among which are intestinal parasites, especially ascaris lumbricoides, as well as others.

O'Byrne's case was a five-month-old girl who was first seen because of gastro-intestinal allergy. Both parents were allergic. The child was sensitive to various foods, particularly cow's milk, soy bean, and orange juice. At the age of seven months she was hospitalized because of fever of 101 F., mild diarrhea, and fairly severe anemia. Roentgenograms showed what appeared to be a rather widespread bilateral bronchopneumonia. This changed in position and intensity over a period of ten weeks and at no time were physical signs present in the lungs. She had a severe anemia on admission with a red blood cell count of 1.9. The white blood cell count varied between 1,700 and 7,600; neutrophils 10 to 76 and eosinophils 8 to 50 per cent.

Clinically the patient was apathetic, moderately dyspneic, and at times slightly cyanotic. Response to sulfonamides was unsatisfactory. Penicillin and streptomycin were not then (1940) available. It was three weeks before her temperature became normal. Laboratory studies, except as indicated above, were completely negative including examination of the stools for parasites. Sternal puncture showed normal marrow. The child did well on Mullsoy and gradually overcame her allergy.

ATOPIC DERMATITIS

Atopic dermatitis is the most important skin disease of infancy and childhood. Its treatment from any standpoint, as discussed by Glaser,[34] is not completely satisfactory, but treatment should be carried out because there is no way of determining in advance which child will or will not outgrow the disease and because it is possible, though not yet proven, that such treatment may be a prophylactic measure for preventing the development of other allergic diseases. Breast feeding of the newborn in allergic families is probably an important prophylactic measure. Inhalants and contactants as well as foods may be causes of atopic dermatitis. While evidence is presented to the effect that house dust is not a cause of atopic dermatitis, yet this should be routinely avoided as a prophylactic measure against respiratory allergies. Soap, feathers, wool, animals with fur or feathers, and clothing dye should be routinely avoided. The avoidance of wool clothing, particularly difficult in the winter, is now being made much easier by the use of spun glass fiber insulation in cotton clothing.

Soap should not be used in bathing. Certain soap substitutes, particularly those derived from the newer lauryl alcohol wetting agents are useful. Colloidal baths, (bran or cornstarch) are also helpful. Before local treatment is started, any infection must be cleared up. The treatment of the eczema then depends upon its stage. In the acute, soaks with Burow's solution, 1/20, or potassium permanganate 1/5,000-1/10,000 may be used. Saturated solutions of boric acid are useful but should not be used long or extensively as boron poisoning from this has occurred. The painting of oozing areas with 3 to 4 per cent aqueous solution of gentian violet is also very useful. The 1-2-3 ointment (Burow's solution 1 part, anhydrous wool fat 2 parts, and paste of zinc oxide without salicylic acid 3 parts) is a most useful preparation to apply during the acute stage. In the subacute or chronic stage tar is the most effective local medication. The so-called "white tars" are satisfactory. Vioform in a 1 to 3 per cent ointment base or compound resorcin ointment, N. F., is often very useful. Swartz ointment (4 per cent mercurochrone with 6 per cent salicylic acid, water sufficient to dissolve and anhydrous wool fat and petrolatum, of each sufficient to make 2 grams) is helpful in chronic stubborn patches.

An elimination diet may be constructed from the following ingredients, depending upon the age of the patient: cow's milk substitute (soybean milk or a milk substitute whose protein base is meat[33]); one single pure cereal, as oatmeal; two vegetables; two fruits; one meat (chicken—use capon or rooster); vitamins A, D,

and C in relatively non-allergic forms as "Provatol" (Wyeth) and "Cecon" (Abbott). The feeding of unsaturated fatty acids in the form of soy oil, linseed oil, and lard may possibly be of help.

Direct skin testing by the scratch method may be useful. Intradermal tests should not be done unless preceded by negative scratch tests. Passive transfer tests are necessary where the skin is generally involved or otherwise unsatisfactory. Pyribenzamine and Benadryl administered orally are occasionally of help in relieving itching. Phenobarbital is occasionally helpful and in very severe cases demerol is invaluable.

While all children with atopic dermatitis should not be vaccinated against smallpox and vaccination should not be done on children from homes in which there are unvaccinated children with atopic dermatitis because of the danger of generalized vaccinia, one should not neglect the immunization of children with atopic dermatitis against diphtheria, pertussis and tetanus. Eczematous children should also avoid persons with herpes because they are particularly susceptible to skin infections with the virus of herpes resulting in Kaposi's varicelliform eruption.

The nature of this discussion prevents inclusion in an abstract of many highly specific and important details so that the original article must be consulted.

Ellis-Brown,[23] in a comprehensive review of the subject, states that the commonest cause of allergic eczema is thought to be sensitization of the skin to lactalbumin which acts as a primary antigen provoking the formation of secondary antigens. Eczema is three times as frequent in male infants as in female and is commonest during the dentition period, between the fourth month and the third year. The onset of eczema often coincides with weaning to cow's milk or immediately following vaccination which appears to sensitize the skin and will also cause the smallest patch of eczema to spread widely. (In many years of treating allergic children the reviewer has only once seen eczema exacerbated following smallpox vaccination.) Ellis-Brown further states that retention of chlorides with great and rapid fluctuations in the water content of the tissues occurs in eczematous infants, and the periodic exacerbations of pruritus and eczema are said to correspond to the times at which there is retention of water with accumulation in the skin. Diuresis and loss of weight follow the exacerbation with improvement of the skin condition. Diarrhea, starvation, or pyrexia, especially the latter, also cause clinical improvement. Chronic atopic dermatitis (Besnier's prurigo) is due to sensitization of the skin to antigens which are absorbed from the alimentary tract and escape fixation and destruction in the liver. These antigens, which are non-protein in nature and of simple composition, are not eliminated by the liver. It is this failure to eliminate rapidly these protein derivatives from the circulation and the reaction of these with antibodies in the skin which expresses itself as eczema. These reactions are protective in function as they result in the fixation and destruction of the circulating antigens. The skin therefore attempts a vicarious protective function when the liver has failed.

Seborrheic dermatitis results from infection of the infant with pityrosporon caught from the scalp of the mother. Other types of eczema are provoked by external irritants and other skin infections.

As far as treatment is concerned, the author advises the omission of milk as far as possible to avoid lactalbumin. If the infant is breast fed, one must be sure that the mother's diet is well balanced and adequate in calcium and vitamins. The infant should be allowed to nurse only about five minutes at each breast in order to be sure that the child will not be overfed. If the child does not do well, it is necessary to wean the child entirely and substitute for the breast milk some preparation completely free of lactalbumin. Lactic acid milk and hydrochloric milk are often helpful. Restraint is advised to prevent itching. Chloral hydrate and bromide 2 grains of each per year of age in syrup of orange and water are given every four hours for restlessness. Overheating should be avoided. Cotton should be worn in

the summer and silk or linen in the winter next to the body in place of woolen garments. (The reviewer believes that silk should be routinely avoided because of the great frequency with which positive skin reactions are obtained to silk and its clinically irritating properties in these infants.) The child should be bathed in water or preferably in isotonic saline solution but soap should not be used. There are many other highly detailed suggestions for treatment in this paper which cannot be readily abstracted.

Ratner[65] emphasizes the fact that occasionally the eczematoid dermatoses of infants and children may be mistaken for some other disease, as scabies for example. The average age of onset of eczema was found to be 1.9 months and the average age at the time of his observation was 6.5 months. Positive skin tests were obtained in 85 per cent of the patients under one year of age. One hundred per cent of the positive reactors were sensitive to foods but only 41 per cent reacted to foods alone, and 59 per cent reacted to a combination of foods, inhalants and contactants. Ratner believes that contact dermatitis and atopic eczema do not differ in their basic mechanism and should be studied and treated on the basis of antigen-antibody interactions. They differ only in the mode of sensitization, so-called atopic eczema usually resulting from intrinsic contact with antigens and contact dermatitis from extrinsic contact. In feeding these children Ratner employs his so-called "allergenically denatured diet" containing foods in which the albumin and globulin fractions have been coagulated by heat. In this diet he includes such foods as evaporated milk and hard-boiled egg. (The reviewer would like to point out that as far as these two particular foods are concerned Ratner stands alone among pediatric allergists in considering that they are reasonably safe for the eczematous infant.) The infant may be sensitized *in utero* to foods in which the mother overindulged or may acquire allergens through the breast milk.

Many excellent directions for treatment are given and the article must be studied in detail to learn these. If one consults the United States Dispensatory he will find practically every ointment in common use, and by a proper utilization of this information, ointments can be created to fit the needs of the individual. Environmental control with avoidance of dust, feathers, wool and fuzzy clothing is stressed. Local infection of the eczematous skin must be cleared. Mycotic involvement is not common. Boric acid preparations are best not used because of their potential toxicity. Unlike practically all other pediatric allergists, Ratner feels that bathing with a bland soap and water is not contraindicated. Sedatives are of great value, particularly phenobarbital in 15 mg. (¼ grain) doses and aspirin in doses of 0.2 to 0.3 Gm. (3 to 5 grains). A combination of the two is often most effective. If the child has retardation of bone age as indicated by roentgenograms of the wrists, thyroid should be cautiously administered. Unsaturated fatty acids as provided by lard, linseed and soy bean oil can do no harm and may help. No eczematous child should be vaccinated against smallpox. Sulfonamide and antibiotic ointments should not be promiscuously used in secondary infected eczema because of the possibility of sensitization to these drugs, but they may be used if a real indication exists. Benadryl and Pyribenzamine may help allay itching to some extent. They have no specific effect upon the eczema.

Perlman[56] comments upon the fact that so little real progress has been made in the management of infantile eczema. All forms of eczema begin as an erythema which may progress to edema, vesiculation, exudation and crusting. The histological pathology and the correlated treatment of eczema are discussed in detail. Rest is important and the author does not hesitate to use splints. The sedative of his choice in phenobarbital 15 to 30 mg. (¼ to ½ grain). Pyribenzamine and Benadryl are sometimes helpful for the relief of itching. Ordinary soap and water should not be used. Starch baths and lanolin baths are most helpful. The removal of offending

allergens is best carried out on the basis of observation and elimination diets rather than skin testing. No treatment should be permitted which is injurious to the general health of the infant. The guide to success in the use of topical remedies is conservatism and simplicity. The treatment of eczema depends upon the stage. In the acute stage are recommended soaks of boric acid solution (2 per cent or one-half saturated); Burow's solution (1 part to 30 parts of water); silver nitrate (1/8 to 1/4 per cent); potassium permanganate (1 part to 10,000 to 30,000 parts of water); infusion of chamomile tea. For the subacute stage the following are recommended: Lassar's simple zinc paste (without salicylic acid) which may be used as vehicle for phenol, menthol or benzocaine; evaporating shake lotions containing zinc oxide, magnesium carbonate or talc in various combinations or zinc oil (40 parts of zinc oxide plus 60 parts of olive oil). For the chronic stage the author employs tar, 1 to 10 per cent; ichthammol, 3 to 6 per cent; tar ointment, N.F., 25 to 50 per cent; crude coal tar, 6 per cent or full strength; naftalan, 1 to 10 per cent in ointment or lotion; salicylic acid 3 to 10 per cent may be added as a keratolytic if necessary.

The details of many other topical remedies are given. If everything else fails roentgenotherapy should be tried very cautiously. This presentation is a mine of information which must be read to be appreciated.

Ross and Brown[67] state that skin testing is unsatisfactory in infants under five months of age. They test chiefly by the intradermal method. Their experience with soy bean as a substitute for milk does not appear to have been particularly satisfactory. Elimination diets are helpful. Besides foods, eczema may be due to inhalants or contactants such as house dust, tobacco, feathers, and wool, and such cases may be treated by the injection of the specific antigen. They also treat food sensitivity by the injection method. (The abstractor notes that this procedure is not recommended by any leading pediatric allergists in this country.)

For local treatment the authors recommend restraint and the clearing up of local infection. Wet starch poultices are used for moist surfaces. They have used the following ointment with very gratifying results:

Crude coal tar	2.5 per cent
Titanium dioxide	7.5 per cent
Metaphen	1.0 per cent
Butesin	1.0 per cent
Zinc oxide	7.5 per cent
Hydrosorb (Abbott) qs ad	100.0 per cent

The tar may be increased to 5 per cent in the more severe cases. According to the authors' records one-third of atopic eczematous children will develop other allergic manifestations in later life. Care should therefore be taken in these children to avoid environmental allergens to which a child may be easily sensitized.

Three interesting and important contributions to the study of infantile eczema have been made by Wolpe. One of these[84] is a study of the management of infantile eczema at the Los Angeles County Hospital. Here eczematous children are cared for as far as possible in the outpatient rather than the inpatient department. Fairly uniform dermatological management is exercised. Restraints for the control of itching are recommended and since itching often persists for some time after the skin has apparently completely cleared, these should be continued for at least two or three months after itching has ceased. X-ray film from which the emulsion has been removed and cleaned and re-oiled with mineral oil every four hours is placed beneath the infant's head. (The reviewer, who used to employ such films, now uses plastic sheets, as Koroseal, which are easier to obtain and to handle and more comfortable because more flexible.) The position of the infant should be changed several times a day. Exacerbations of eczema occur with almost any metabolic upset as upper respiratory infections, teething and diarrhea. Eczematous infants are easily

dehydrated and fluids must be kept up by gavage or parenterally if necessary. Sodium phenobarbital is used as a sedative when necessary, and Pyribenzamine in doses of 3 to 4 mg. per pound per twenty-four hours has been found to relieve itching in a large number of cases. Variety by means of rapid alteration of the diet is urged. Intolerance to vitamin preparations is frequently encountered and these are best tested one by one. Drisdol and ascorbic acid are recommended and vitamin B complex derived from rice has proven less allergenic than that derived from yeast.

The tables published in this article contain a great deal of useful information regarding environmental control, methods of restraining the infant, dietotherapy and local therapy.

Another study[83] concerns 284 infants in the same hospital who were divided into two groups. All received the routine therapy for eczema but one group was fed milk and the other milk substitutes. The patients fed on milk substitutes obtained clinical relief sooner than those fed on a milk dietary. While both groups showed a substantial weight gain, that of the milk fed group was slightly but not significantly greater. (The use of milk substitutes whose protein base is strained meat[83] was not mentioned by the author.)

Another report[85] concerns blood protein deficiency in infantile eczema. Severe disturbances in nutrition of infants suffering from severe generalized eczema were found to be accompanied by startling blood protein deficiencies. The incidence of this deficiency was found to average 26 per cent in fifty-four unselected cases. The globulin fraction tended to show a greater deviation below normal than the albumin, and globulin deficiency was dissipated more rapidly. It was recommended that routine blood protein studies be made in this disease. Blood protein deficiencies were overcome by the administration of plasma, whole blood, amino acids orally and parenterally, parenteral liver extract, and increased dietary proteins including beef and gelatin. Plasma was given when the total blood protein values were 5.5 grams or below.

Because of the importance of food allergy, substitutes for milk are of great interest and palatability is a prime requisite, especially in milk substitutes designed for older children and adults. Mermis[51] has reported a child with atopic dermatitis who could not tolerate one soy bean formula because of frequent, watery bowel movements. The stools were relieved by goat milk but the eczema became worse. On "Allerteen,"* a new soy bean milk preparation, there was no difficulty with the stools and the eczema disappeared.

One phase of infantile eczema which has not received the attention which it perhaps deserves is the question of the role of focal infection. This has recently been emphasized with respect to infants and children by Chobot[17] and adults by Grove.[37] This subject is of such importance that it is regrettable that these authors have not given details of individual cases. With respect to adults Grove states that in recent years we have come to recognize that the eczema seen in allergic patients is frequently secondary to a sinusitis. These patients are frequently negative on skin testing, both intradermal and patch, and the use of elimination diets has not produced any relief. Upper respiratory infection usually exacerbates skin lesions. These cases may be helped with a vaccine, especially made from the sinus mucous membranes. (The reviewer feels that what holds true for adults may possibly hold true for children. It is a well known fact that it is difficult or impossible to clear eczema when infected unless the infection is treated first. However, the study of infantile eczema from the viewpoint of focal infection is as yet an unexplored field.)

As a result of a review of recent literature Blattner[12] comments that it seems clear that the persistence of cutaneous sensitivity to ingesta may lead to erroneous

*Prepared by the Charles Kilgore Co., Inc., Yonkers 2, N. Y.

interpretation of skin tests and thereby to unnecessary and undesirable dietary restriction of the allergic child.

ECZEMA VACCINATUM

A case of eczema vaccinatum is reported by Rubenstein[68] in a two-year-old boy with atopic dermatitis involving the popliteal and cubital fossae. Vaccinia developed in these areas nine days after an older sibling had been vaccinated. The lesions in the eczematous areas coalesced into a grayish, purulent mass. A few discreet umbilicated pustules were present over the face, lids and in the hair. The mode of transmission of the infection from the vaccinated child to the sibling with atopic dermatitis was not known. The patients had not slept together but there was no attempt at segregation and there was ample opportunity for direct contact between the children. The possibility of droplet infection must also be considered, as the vaccine virus is present in the upper respiratory tract four or five days after vaccination.

The child was hospitalized four days after the onset of the vaccinia. He was quite toxic at times and was treated with sulfadiazine and penicillin. Recovery was uneventful except for the development of a sulfadiazine rash. Healing was completed with no scar formation observed after several months. The diagnosis was confirmed by the Paul test. It is emphasized that vaccination should be deferred on patients with skin disorders until recovery has occurred. Vaccinated persons should not be exposed to patients suffering from skin infections.

Alpern[1] notes a fourteen-month-old white boy who suffered from eczema and asthma. Vaccinia was contracted from a brother who had been vaccinated thirteen days previous to the appearance of vesicles in the infant. The child was hospitalized on the third day of illness at which time a urine examination was normal; the blood showed 5.9 Gm. per cent of hemoglobin with a white count of 51,000 with 49 per cent eosinophils. Treatment included transfusion, penicillin, sulfadiazine, intramuscular injection of gamma globulin and the usual supportive measures. The patient died four days after admission and at necropsy an extensive pulmonary process, not suspected during life, resembling an aspiration pneumonia was found. In discussing this case Dr. P. V. Wooley, Jr., stated that in rabbits the use of human immune serum would prevent a take when injected during the incubation period and would prevent metamorphism when used in the papular stage but the course of the primary take could not be influenced thereafter. Subsequent to this case two other patients with eczema vaccinatum were seen and these survived. Neither, however, had the widespread confluent lesions seen in the patient who died.

(The reviewer notes that the whole picture of treatment of generalized vaccinia has changed for the better since the introduction of sulfonamides and penicillin. Since these have come into general use, very few deaths have occurred from vaccinia.)

Fries, Borne and Barnes[30] have reported sixteen cases of Kaposi's varicelliform eruption due to vaccinia virus complicating atopic eczema. These were part of a unique outbreak of forty-three, the first epidemic to be reported in the United States. This occurred in New York City during May, 1947, following a mass vaccination campaign against smallpox. The varicelliform eruptions started with dramatic suddenness three weeks after the beginning of the campaign and ceased with equal abruptness five weeks after the campaign was over. The incubation period varied from five to nineteen days with an average of 10.6 days. The infants were admitted two or three days after the onset of the eruption at which time the constitutional symptoms, mild at the onset, suddenly became severe with the appearance of high fever, restlessness, irritability, facial edema and in all cases intense pruritus. There were three phases to the course of the disease—the acute febrile, the healing and the convalescent, each of about one week's duration. The fever generally

dropped by lysis. The eruption was confined almost entirely to the eczematous areas. Regional lymphadenopathy was marked. An impressive manifestation during the febrile period was the marked regression of the eczema. Roentgenograms were made in all but one patient and seven showed bronchopneumonia. Alopecia occurred in ten patients and varied from slight to complete loss of hair. Local treatment was with 1/20 Burow's solution. Penicillin 50,000 units was administered intramuscularly every three hours until the patient was afebrile at least forty-eight hours.

Eleven of the cases were in children under two years and the remainder seven years of age or less. Thirteen children were Negro and three white, the predominance of the former probably due to poorer living conditions. Thirteen were males (80 per cent). There were no deaths in this series but the mortality for the forty-three patients in New York City was 4 per cent. Fifteen of the author's series were vaccinated against smallpox about four weeks after admission with resulting immune reactions.

Ruchman, Welsh and Dodd[69] have reported four cases of Kaposi's varicelliform eruption in patients with atopic dermatitis. Three occurred in adults and one of these was fatal. One occurred in an infant fourteen months of age. In all instances there was a definitely known exposure to herpes simplex five to ten days before the onset of the eruption and no history of exposure to vaccinia virus. The virus of herpes simplex was isolated from the cutaneous lesions of all four patients.

CONTACT DERMATITIS

Dermatitis due to "finger paints" has been reported by Tobias.[77] A child, eight years of age, developed an acute erythematovesicular dermatitis in the interdigital spaces of his right hand four days after using finger paints. These are variously colored water-soluble creamy preparations which may be applied with the fingers or forearms to a specially wetted paper to produce various colored designs. The product is popular with children and has been used by adults in the form of occupational therapy. Three days later, a similar eruption, patchy and linear in character, appeared on the right cheek, mid-forehead, and left forearm where the child had apparently also rubbed the paint. There was mild itching. Patch tests on the patient were positive and on controls were negative. The manufacturer would give no information as to the composition of the preparation so the exact cause of the sensitization was unknown. A plasticizer was suspected.

PURPURA

Jelke[42] describes a girl, three years of age, who was given subcutaneous injection of toxoid for the prophylaxis of diphtheria and developed purpura of the Schönlein-Henoch type two days afterwards. The patient was sick for five months during which there were numerous exacerbations and remissions of the disease. The author believes that the disturbance should be considered as a true allergy and be termed anaphylactic rather than anaphylactoid purpura.

VULVOVAGINAL PRURITUS

Mitchell and associates[52] have reported eight cases in children, four to eleven years of age, of vulvovaginal pruritus associated with hay fever. In each case the history of vulvar itching was voluntarily given as the major complaint. One hundred adult female patients treated for ragweed pollinosis were questioned but no instance of vulvar itching was discovered.

There were no visible local changes except those as a result of the scratching. The most intense itching appeared to be in the region of the mucocutaneous junction between the vulva and the vagina. Itching occurred only during the ragweed

pollinating season except in three instances where there was in one case itching during the grass pollen season; in another following the administration of a sulfonamide; and in another after playing with dandelion blossoms. Response to specific treatment, filtered air, or change of climate was proportional to the improvement of the hay fever. The author states that no cases of pruritus ani were encountered as a complication of hay fever (although this may occur as part of a constitutional response to an overdose of pollen) and no instance of pruritus of the urinary meatus. However, in three of fifty-two boys under five years of age, diurnal frequency and nocturnal enuresis were noted at the height of the ragweed hay fever season.

GASTROINTESTINAL AND FOOD ALLERGY

It is taken for granted by many pediatric allergists and pediatricians that the ordinary "three-month colic" in infancy is more commonly due to allergy than to any other factor. While there is no doubt that allergy is the cause in many instances, statistical studies on this subject are lacking and it is readily apparent to anyone who has studied colic that not all cases, perhaps not the majority, can be explained on the basis of allergy nor can such cases be relieved by allergic treatment in the majority of infants. An important contribution to this subject has been made by Pierce.[58] He states that the fact that colic usually starts at the age of two or three weeks and ends at about two or three months could be adequately explained by considering that a developmental factor is at least partially responsible for the disturbed physiologic mechanism which causes the symptom complex. He reports three cases, selected from a larger number of premature infants, who had been quiet and progressing normally. These infants, when approximately two weeks older than the expected date of delivery, manifested excessive crying for a period of several weeks. This behavior was not explicable on the basis of improper feeding techniques or hunger. The crying seemed to appear when the infants reached a certain stage of maturity. The author states that there are many factors such as improper feeding, gastrointestinal allergy, autonomic imbalance, and others which may be partially responsible either alone or in combination with others for the colic. However, the evidence which he has presented indicates that a developmental factor may also contribute.

Hypertrophic pyloric stenosis is another disease of particular interest to the pediatric allergist since the original report of Balyet and Pounders[8] on an infant with all the signs and symptoms of this disease which was eventually explained on the basis of food allergy. Bendix and Nechels[11] studied seventeen adults who had been operated on for hypertrophic pyloric stenosis. In the case of only one patient, a man twenty-five years of age, is allergy mentioned and in this case both the father and the mother of the patient were allergic. However, migraine is well represented in the family history of many of these patients. A tentative theory is submitted that hypertrophic pyloric stenosis is due to an autonomic imbalance plus a local irritation during embryonic life.

Various manifestations of gastrointestinal allergy are discussed by McLendon and Jaeger-Lee[50] who also state that not all colic is of allergic origin. They reported particularly on the role of cow's milk in the gastrointestinal allergy of children. One interesting case is mentioned in which the infant was sensitive to the yeast used in the cow's milk substitute; in other instances the irradiation of milk by ultraviolet light was the cause of unknown changes in milk, with resulting symptoms of "colic" in many infants. Persistent constipation with intermittent periods of diarrhea occur. This is frequently caused by cow's milk. A variety of other disturbances, as underweight, failure to gain, pallor, lassitude, fatigue, poor school progress, irritability, halitosis, frequent colds, abdominal pain or distress, nausea or vomiting, and intermittent bouts of fever, may all be on an allergic basis.

Skin testing is of little value but occasionally helps. The history is the most important means of arriving at a workable diagnosis. Five case reports illustrating some of the above conditions due principally to cow's milk are given in detail. The absence of milk from the diet over a period of years does not lower the blood calcium or phosphorus nor does this result in increased dental caries.

(The reviewer notes that halitosis may be caused by milk or milk products but this is commonly due to a metabolic defect involving the liver resulting in the liberation of certain malodorous fatty acids through the expired air. This cannot be considered as an allergic phenomenon. If a child is placed on a milk-free diet, it is important that adequate calcium and phosphorus be supplied from other sources because if the body does not have an adequate intake of these minerals, skeletal and other defects are certain to follow.)

Rinkel[66] has made the observation which is exceedingly important, if confirmed, that in the use of therapeutic diets in allergy cumulative reactions are not as important as the maintenance of tolerance and the prevention of the development of sensitization. In selecting foods for the diet only those for which the patient has a tolerance should be included. The factors to be considered are: (1) whether the food has ever been a cause of symptoms, and (2) if the patient has a high or low tolerance to foods in general. The foods are used at intervals of two to seven days, taking one normal serving per day at one meal only.

Whenever a patient is proved sensitive to a food, it is omitted until tolerance develops, usually a matter of three to eighteen months. The food is checked for tolerance at three months and retested at nine months if symptoms followed the first test. Another test is made at the end of a year and if there is still a reaction, the final test is made at eighteen months. If this test is followed by symptoms, it is best to consider the food as a permanent food allergy and discard it. If the food fails to produce symptoms, it is used once a day at five-day intervals for six feedings. If symptoms do not occur, the food may be used once every three days and after three months every two days.

There are very few foods which have been allergens that can be used after tolerance has been achieved by elimination, at intervals of less than once in three days. However, even when a food is used only once in three days the patient may become resensitized. These allergies are insidious and difficult of detection and when the offending food is discovered, if used again the intervals must not be closer than once in six days.

A food which causes eczema in a baby does not necessarily cause asthma in childhood when the patient has become asthmatic. There is no food which, after tolerance has been obtained, may be replaced in the diet and used with the same frequency as before the sensitization was proved, without the allergy recurring.

The rotary diversified diet may be used in infants potentially allergic as a prophylactic measure. Wheat-sensitive patients easily become sensitive to corn so that in these patients the status of corn as regards tolerance must be determined. When the diet fails to produce the desired result, deliberate individual food testing is indicated. Three detailed case reports are included.

Chobot[17] observes that under no circumstances should an attempt be made to hyposensitize a child by injection to a food to which he reacts as 98 per cent of children lose their food sensitivities by the time they are five years of age.

Slobody, Untracht and Hertzmark[71] have made a study of rice sensitivity in children. A detailed review of the literature regarding allergy to cereal indicates that the incidence of allergy to rice is about 0.22 to 0.32 per cent, or roughly one in 300 to 450 of the general population; for children about one in 170 to 240. For purposes of checking this estimate , 174 normal healthy children and hospitalized boarders were tested for hypersensitivity to extracts of cereal proteins. Those cases giving

a positive reaction to rice were intensively checked clinically for rice intolerance. Two children reacted with definitely positive skin tests to rice extract; one with a wheal 2 cm. in diameter and the other 1.5 cm. Six other children gave equivocal skin tests. None reacted clinically on being fed cooked rice. The authors assume that the cooking of the rice in the presence of moisture renders it non-allergenic as suggested by the work of Ratner and Gruehl.[64]

(The reviewer notes that it is a well known fact that some children who are wheat sensitive cannot tolerate Pablum because of the wheat which this contains, even though the preparation has been thoroughly cooked in the presence of moisture. There would therefore appear to be no justification for the assumption that rice is innocuous from the allergic standpoint because it, too, has been cooked in the presence of moisture. To prove this clinically as opposed to the assumption that because sensitized guinea pigs cannot be shocked with cereals cooked in the presence of moisture, the same applies to human beings, one would have to test children known to be clinically sensitive to rice by feeding rice cooked in the presence of moisture. Since the authors found no such children, they were unable to perform this experiment. The very interesting studies of these authors should be repeated in oriental or other populations where the staple cereal is rice.)

The first case of allergy to fennel has been reported by Levy.[45] This food is a member of the Umbelliferous family which includes dill, carrots, celery, parsley and parsnip. It is cultivated chiefly for its aromatic leaves and seeds and for the enlarged basis of its leafy stalks which are eaten boiled. The seed is commonly used by Italians as a condiment and it also has certain medicinal uses. Levy's patient was a nine-year-old Italian boy with ragweed pollinosis and ragweed asthma. He reacted to fennel extract on direct skin testing and a passive transfer. Asthmatic attacks were produced by eating foods containing fennel.

DRUGS AND DRUG REACTIONS

The passage of drugs through breast milk and through the placental circulation is of interest to the pediatric allergist because of the possible allergic reactions to these drugs which may occur in the newborn as well as for other reasons.

Houts[41] has reviewed the literature concerning the excretion of common drugs in breast milk. There is no evidence that alcoholic beverages taken by a nursing mother may affect the infant. Habitual and excessive smoking on the part of the mother does not appear to have a harmful effect as far as the transmission of nicotine through breast milk is concerned. Aloin, calomel, phenolphthalein, rhubarb, and senna when taken by a nursing mother in therapeutic doses do not have a laxative effect upon the infant. Cascara, however, will normally pass through the breast milk and affect the infant clinically.

As far as sedatives are concerned, codeine, demerol, morphine and opium appear to be harmless. Bromides taken by the nursing mother may produce their therapeutic effects in the infant. Barbiturates, especially when given in large doses, may be transmitted and affect the infant.

Sulfonamides taken by the nursing mother pass through the breast milk in traces insufficient to produce therapeutic effects in the infant but probably in sufficient quantities to produce effects if the infant happens to be sensitive to the drug. The same is essentially true as regards penicillin. Sodium salicylate and quinine may be taken by the nursing mother without harm to the infant. There is some experimental evidence that the metals arsenic, lead, and mercury, may be transmitted through the breast milk.

Perlstein[57] has described the case of an infant delivered by Caesarean section from a thirty-four-year-old mother who was averaging 10 grains (0.65 Gm.) of morphine intravenously daily. The child weighed 7 pounds 5 ounces (3,317 Gm.) at

birth and appeared normal. On the third day the infant was restless and irritable and passed liquid stools. By the fourth day she had lost weight and had generalized tremors. Examination of the blood showed no morphine. The vernix caseosi had been preserved and showed a positive qualitative test for morphine. The treatment consisted entirely of sedation with phenobarbital (⅛ grains) every four hours and this allayed all symptoms.

It has been known for some time that morphine passes readily through the placenta in sufficient quantities to cause addiction in the fetus. The author quotes Sollmann[73] to the effect that morphine is not excreted in the breast milk.

DELAYED REACTION TO PENICILLIN IN BEESWAX AND PEANUT OIL

Mandel, Basch and Greengard[49] report the case of a girl who had been breast fed as an infant and whose past history was negative except for an eruption accompanied by fever and diarrhea at the age of three months. This was attributed to the repeated ingestion of Roquefort cheese by the child's mother. The child had never had any antibiotic medication until at the age of three and one-half years because of a respiratory infection she was given daily injections of 0.5 c.c. of calcium penicillin in beeswax and peanut oil for three days and 100,000 units of sodium penicillin by mouth during the course of one day; a total of 550,000 units of penicillin in four days. Recovery from the infection was prompt, but swelling, erythema and induration developed about the sites of the intramuscular injections and persisted for some days.

Three weeks after the cessation of treatment the child awoke with fever, marked cervical lymph adenopathy, and a slight generalized pruritus followed by an erythematous and morbiliform rash, urticaria and angioneurotic edema. There was anorexia, nausea and vomiting. A blood count at this time showed 24 per cent eosinophils. At the height of the fever and eruption, aspirin gave more relief from discomfort than did Benadryl, but the Benadryl gave more relief of the urticarial symptoms. Recovery was complete twenty-six days later except for residual exfoliation and mild itching which persisted another month. Two weeks after complete recovery skin tests were done with various penicillin preparations. These were negative except for moderate erythema about a scratch test with the penicillin in oil and beeswax which developed in ten minutes and faded in an hour.

Systemic reactions to penicillin may be either immediate or delayed, the latter commonly occurring within two weeks after administration of the drug. These reactions appear to be less frequent in children than in adults and are usually immediate. The delay of symptoms in this case for twenty-one days after termination of the therapy is unusual, both for adults and children. It is generally assumed that reactions to penicillin in oil and beeswax are due to the penicillin content. It is highly unlikely that the ingestion of Roquefort cheese by the mother had anything to do with sensitization of the child to penicillin.

(The reviewer has seen several cases where, following fairly severe reactions to penicillin in oil and beeswax, the penicillin therapy was continued with the crystalline product in aqueous solution without trouble. The relationship between penicillin sensitivity and the ingestion of Roquefort cheese has not yet been worked out. Some of the molds in this cheese belong to the penicillin group and it would thus appear that such acquired sensitivity to penicillin from eating Roquefort cheese is at least within the realm of possibility.)

ANTIHISTAMINICS

The use of the antihistaminics in bronchial asthma has been discussed above. Levin[44] feels that these drugs are of definite value in infantile eczema for the relief

of the itching, but admits that it is difficult to know if the relief is because of the sedative effects or because of its antihistaminic effect.

Lockey[46] describes seven cases of atopic dermatitis, all less than six years of age, who were given from 12.5 to 25 mg. of Benadryl four times a day for an average of eleven days. There was some slight improvement in two cases, attributed to a diminution of the itch reflex. None of the cases cleared. Friedlander,[29] in reporting on the parenteral administration of Benadryl, mentions a year-old infant suffering from a severe penicillin reaction who was benefitted remarkably by intramuscular injections of from 5 to 10 mg. of Benadryl every four to six hours over a period of a week.

Duerfeldt[21] has reported the case of an acute Benadryl poisoning. The patient was a white girl three years old who had never had any allergic symptoms. She swallowed fourteen to sixteen capsules of Benadryl 50 mg. size (700-800 mg.). About fifteen minutes later she developed ataxia, laughed unduly, had twitching movements of her face and picking movements of the hands, did not obey requests, stiffened in a convulsive manner when picked up, had blurred speech, and dilated pupils. The empty capsule box was discovered, vomiting was induced, and several pieces of pink gelatin were recovered. About thirty-five minutes after taking the capsules, she became drowsy, developed generalized convulsions, became limp and gray, and stopped breathing. She was revived with artificial respiration, became hyperactive with muscular twitching alternating with marked periods of depression and sleepiness. Dilaudid 2 mg. was given with only partial relief of the convulsive movements which were finally controlled with 30 c.c. of 50 per cent ether in olive oil rectally. Respiratory collapse without preceding cyanosis occurred four times in the following three and one-quarter hours but responded to artificial respiration, at one time administered for four and one-half minutes.

Histamine, 3 mg., given intramuscularly was followed by marked flushing of the neck, shoulders and chest, which faded after about two hours. Asthmatic breathing was noted about forty-five minutes after the histamine had been given and repeated doses of adrenalin were required to control this. Coramine was given intramuscularly. That evening, eleven hours after taking the capsules, the pupils were still widely dilated, the face twitched, and she was unable to stand. The following day she was still ataxic and drowsy and had a slight fever. These symptoms gradually disappeared in about four days.

The amount of Benadryl taken by this girl was about 55 mg/Kg., about twice the lethal dose for dogs when administered intravenously. A report to the author from Dr. E. A. Sharpe of the Parke-Davis Company stated that "one teen-age girl is reported to have taken thirty of the 50 mg. capsules with successful suicidal intent," and "that an asthmatic patient sixty-five years of age misunderstood directions and took fifty of the 50 mg. capsules at one time but survived."

It is pointed out that the attractive appearance of the red Benadryl capsule with the white band may induce children to swallow these and the parents should be warned of that danger.

Pipes[59] has briefly mentioned a ten-year-old boy with perennial allergic rhinitis who developed a rash following the use of Pyribenzamine. He did not mention whether the elixir or the tablets were used or whether the excipients were individually checked to determine their possible role. It will be recalled that Brown and Crepea[15] reported a man with asthma due to gum tragacanth used as an excipient in Pyribenzamine tablets.

Baker* reports the case of a five-year-old boy with an allergic skin reaction consisting of papules and vesicles accompanied by extreme itching, cough and rhinitis. Benadryl gave no relief and one tablet of Pyribenzamine (50 mg.)

*Baker, Julia—personal communication to the author.

likewise had no effect. The boy was then given one tablet of Pyribenzamine every three hours during the day and two tablets at bed time. He was awake and delirious all that night chattering or whispering and waving his hands about. Flowers looked like bulls' heads. Everything seemed to be moving. The medication was not continued; he vomited the following morning and a few hours later appeared normal except that the severe itching had recurred.

PRIVINE

Greenblatt[36] has reviewed the cases of Privine sensitivity, reported in these columns in 1944 and 1947,[31] and has added three additional cases. He points out that while sedation resulting from the use of Privine nose drops in the dosage recommended may be regarded as true hypersensitivity, if symptoms result from the ingestion of larger amounts of the drug, this cannot be classified as hypersentitivity, although the resulting syndrome presents similar symptoms.

The first case was a boy two months of age who was given three drops of the 0.05 per cent Privine solution into each nostril for rhinitis. One-half hour later the mother noted that he could not be aroused. He was pale and limp with shallow respirations thirty per minute. He would jerk his head from side to side several times a minute and gasp. The heart rate was 100 per minute; the rectal temperature normal. He would utter a faint cry when spanked. There was no cyanosis at any time. He was hospitalized and stimulated with 0.2 c.c. of coramine solution and 0.10 c.c. of adrenalin. Inhalations of 95 per cent oxygen with 5 per cent carbon dioxide were given. He would cry vigorously a half hour after these were started but would lapse into lethargy and jerk his head intermittently. The symptoms gradually disappeared and he was normal six hours afterwards. The family history was negative for allergy except in a brother as noted below. The physical examination was otherwise negative except for moderate anemia.

When the above incident occurred, it was remembered that a brother of this boy who was a Mongolian idiot with a cardiac defect, had some time previously been given three drops of Privine 0.05 per cent into each nostril at the age of one and one-half months because of rhinitis. He became limp, hardly breathed, and was hospitalized. However, under stimulation, recovery occurred in a short time. At this time (1944) Privine sensitivity was not recognized and the condition was thought to be due to his congenital defects as a result of which he died not long thereafter.

Another case is mentioned of a fourteen-month-old boy who swallowed 7.5 c.c. of 0.1 per cent Privine and then slept for twelve hours. His temperature was subnormal. He was treated by the administration of caffeine and warmth and made a complete recovery.

Hainsworth[38] reports the case of a twenty-two-month-old white boy who accidentally swallowed about 3 or 4 c.c. of an 0.1 per cent solution of Privine. According to the boy's weight, this was calculated to be about 300 times the effective therapeutic dose for an adult when the drops are administered intranasally. The principal systemic manifestations were low temperature; fretfulness; cold, pale, clammy skin; lethargy; bradycardia following initial tachycardial, diaphragmatic, gasping, irregular and almost imperceptible respiration and high blood pressure (170/150). Treatment was symptomatic. The total duration of symptoms was about fifteen hours. The child began to improve in about nine hours.

The main pharmacologic action of Privine is to elevate the blood pressure by peripheral vasoconstriction. It also causes cortical stimulation followed by depression and depresses the basal centers somewhat similar to that which occurs in phenobarbital poisoning.

MISCELLANEOUS DRUGS

Dundy, Zohn and Chobot[22] treated twenty adults and twenty children with allergy with Hapamine (histamine azoprotein). Therapy was instituted by subcutaneous injections beginning with 0.05 c.c. and increased weekly by 0.10 c.c. until a maximum dose of 1.00 c.c. was reached when possible. There were two treatment reactions among the twenty children. One had to be discontinued because the patient vomited regularly within two hours of the injection; in the other child the drug had to be stopped because of marked recurrent local reactions. The drug was found to be generally ineffective in all the allergic conditions for which it was used and severe local and some general reactions occurred in about 10 per cent of the cases. The authors also could not detect any diminution in the whealing capacity of the skin following the treatments with Hapamine.

Lowenberg[48] reported the case of a boy eleven years old who had taken tincture of Rhus toxicodendron orally for the prophylaxis of poison ivy. Medication had been taken irregularly in fairly large doses, occasionally as much as 57 drops (3.5 c.c.) at a time. An intermittent fever developed which reached 109.2° F. The onset was with headache, nausea, and vomiting of twenty-four hours duration. There were also pulmonary signs suggestive of pneumonitis, and evidence of gastric hemorrhage and damage to the central nervous system resulting in severe convulsions and disturbance of the temperature regulating mechanism. A hemorrhagic encephalitis was suspected. After a stormy illness, complete recovery occurred in about two weeks. The literature regarding reactions to the oral administration of tincture of Rhus toxicodendron is reviewed and caution is urged in its use.

Mesantoin (methyl-phenyl-ethyl hydantoin) is a new anti-convulsant said to be particularly effective in the treatment of grand mal seizures. Ruskin[70] describes a girl ten years of age with this disease who had a history of repeated cutaneous reactions to various drugs including anticonvulsants who was given 0.3 Gm. of Mesantoin daily. After twelve days, she developed a fulminating bullous dermatitis which was accompanied by a progressive drop in the white blood cell count. Death occurred about two weeks after the onset of the rash. There was no necropsy. It is concluded that extreme care should be exercised in the use of this drug, particularly where there is a history of previous drug rashes.

PSYCHOSOMATIC FACTORS IN CHILDHOOD ASTHMA

The importance of psychologic factors in asthma was accepted without question until the development of the allergic concept early in this century, according to Bakwin.[7] At present the psychosomatics of this disease are again being intensively investigated. The situations which most commonly induce an asthmatic attack are threatened separation from the mother, rage and fear. A mother will commonly report that she is afraid to cross her child lest he have an attack and the child's attacks are increased under emotional strain. On the other hand, relief of an attack following profound emotional disturbance or fright, has been repeatedly reported since the days of Salter.

Parental overanxiety is the rule and this is often transmitted to the child causing him to become apprehensive, overanxious, restless, hyperactive and a poor sleeper. The child is overprotected and his activities limited as with chronically ill children in general. Since these children are often kept indoors in close association with adults from whom they acquire good vocabularies and grown-up attitudes, they may appear mentally superior. Removal from parents and home tensions is often beneficial.

In history taking one should seek information as to the relationship of emotional attitudes towards attacks; the interparental relationships; the personality make-up

of the child and various related factors. Where the emotional difficulties in the home are deep seated, the aid of a psychiatrist should be sought. The object of treatment is to permit the child to live as nearly like the non-afflicted children of his age as possible.

Randolph,[63] in a remarkably fine study, calls attention to the tired, listless, irritable child who has long been a difficult problem for the physician; particularly the child with associated abnormalities of behavior without obvious physical findings. Allergy as a cause of these manifestations has not received the attention it deserves. Long before the development of clinical allergy in the modern sense the syndrome appears to be recognized by Smith Baker.[6] Four illustrative case reports are presented. In one child the symptoms were due to wheat and corn; in another wheat, corn and several other regularly ingested foods; and in two others corn alone. Even such minute amounts of corn starch as occurred in chewing gum, for example, could produce symptoms. Three of the above cases were complicated by clinical evidence of inhalant sensitivity but treatment from this aspect did not relieve the symptoms discussed. Corn sensitivity is highly important and because of the widespread distribution of corn starch and corn sugar, corn sensitivity is easily overlooked. The hyperkinetic and hyperexcited child may also have their symptoms as a result of food allergy.

ELECTROENCEPHALOGRAPHY IN PEDIATRIC ALLERGY

Dees and Lowenbach[20] were stimulated to study the electroencephalograms of allergic children because of the observation of the high incidence of symptoms referable to the central nervous system in these children. An allergic group of eighty-five children ranging in age from two to fourteen years was compared with a large control group. All major forms of allergy, except physical allergy, were represented. Twenty-two patients had a convulsive disorder (petit or grand mal) for which no immediate cause could be demonstrated. These authors make a practice of testing for allergy, patients with cryptogenic convulsions whose personal or family history suggests the possibility of a convulsive disorder.

Occipital dysrhythmia was present in forty-two of the eighty-five patients or about 50 per cent of the group. In the sixty-three allergic children without convulsive disorders occipital dysrhythmia was present in twenty-nine (45 per cent). The over-all percentage of predominantly occipital dysrhythmia was 59 per cent in the convulsive group. A positive family history was associated with occipital dysrhythmia twice as frequently as was a negative family history. No similar preponderance of occipital dysrhythmia occurs in normal children. The type of EEG change is unrelated to the kind of allergy, the duration of the disease or a positive or negative family history. The occipital dysrhythmia was not confined to any one allergic condition and there seemed to be no difference between patients with single or multiple allergic disorders.

In thirty-six patients repeated EEGs were made at various intervals, usually three months to four years. The records were unchanged in twenty-five and showed improvement in eleven. All patients whose EEGs had improved showed improvement in their allergic condition but clinical improvement was found in some without significant change in the EEG.

A trial of dilantin sodium in allergic patients has not as yet been evaluated. The effect of Benadryl was studied in a few patients. After several days this may be followed by improvement in the EEG but within thirty minutes after single doses no effect on the EEG was noted.

The occurrence of abnormal cerebral potential may offer an explanation for the clinical observation that allergic children so frequently present special personality

problems. It is possible that a great deal of such behavior might be explained by a central nervous system which does not function smoothly and efficiently.

GROWTH AND DEVELOPMENT

Cohen and Abram[19] studied the growth patterns of allergic children by means of the Wetzel Grid.[82] This affords a simple, inexpensive and reliable method of following growth and detecting early growth failure. A total of 503 observations were made on 150 allergic patients in private practice and compared with 622 observations on 102 non-allergic controls. The conclusions are drawn that allergy occurs more often in children, especially boys, who by inheritance are constitutionally slender. Active allergy is a common cause of growth failure. Control of active allergy is accompanied by a corresponding growth repair, provided an adequate diet is available.

ALTITUDE AND CLIMATE

Dr. Julia Baker, an American pediatrician practicing in Mexico City, D. F., Mexico, which has an altitude of 7,325 feet, has enlarged on her previous discussion of the subject of allergy in childhood as related to altitude, which was reviewed in these columns in some detail in 1944 and 1948.[31] Her work is of particular importance because to date she is the only pediatrician who has studied this subject intensively. Of 1,000 unselected children, 509 or approximately 50 per cent had allergic symptoms. Evidence is presented that many children with manifestations of allergy in the United States experience exacerbations when taken to Mexico City and many children without allergic symptoms at lower altitudes develop allergic disease in Mexico City, particularly in the case of children where there is a family history of allergy. In these instances the allergic symptoms are unrelated to the race of the patient and are commonly due to foods. While hives are the most clear-cut symptoms, all other allergic reactions may occur, particularly gastrointestinal and respiratory. Seven illustrative case reports are given.

An interesting report by the directors of the Brandes School at Tucson, Arizona, has been published in the letters of the International Correspondence Club of Allergy.[14] This is a private school which has had about 300 students in the seven years of its existence. During the year 1947 the school had sixty-seven students, thirty-seven of whom came primarily because of bronchial asthma; four of these had hay fever. There were sixteen who had allergic rhinitis; six who had chronic sinusitis, and eleven who had frequent recurrent respiratory infections. In the case of many who come on restricted diets it is generally found possible to put the child on the school's regular routine food by the end of the year. In the case of the thirty-seven children with asthma, only one had an attack sufficiently severe to require the services of a physician, except during the Christmas vacation. At this time attacks occurred in three children who were staying at the lodgings of their parents. In each case the parents had more than a suspicion that their presence had something to do with the asthma. Generally speaking the asthmatic attacks decrease in frequency and severity as the school year wears on. Of the eleven children who came to the school primarily because of recurring upper respiratory infectons, nine did well and two contracted what was suspected to be mild scarlet fever. Of the sixteen children who came for allergic rhinitis, their condition also improved steadily as the school year progressed. The authors do not attempt to explain why these beneficial effects were obtained in various types of allergic disease but have merely attempted to state the factual results of their observations.

PROGRESS IN ALLERGY

GENERAL CONSIDERATIONS AND REVIEWS

In a general discussion on allergy in childhood Archibald[4] states that as a rule non-specific drugs are occasionally beneficial but the symptoms practically always return. In general Pyribenzamine and Benadryl are effective in the same patients who do well on allergic management and ephedrine, and fail in the same patients who do not do well on such treatment. (The reviewer notes that there are many exceptions to this statement.) Scratch tests are satisfactory when performed on the back of infants and young children. Patients with respiratory allergies give positive tests in 75 per cent of cases. The most common reactors are, in order: pollens, house dust, cottonseed, cat hair, dog hair, feathers, kapok and pyrethrum. Food tests are the least reliable, the common reactors being, in order: wheat, egg, chocolate, peanut, oat and rice. Skin tests were not done in infantile eczema because they are of so little help clinically. In working out food allergies, diets based on history or on diets of the Rowe type are most successful. The avoidance of house dust is stressed. Infections should be treated conservatively. Vaccines are difficult to evaluate. The indications for adenotonsillectomy are the same as in the non-allergic child. Allergists as a group have tended to underestimate psychological factors. Allergic children up to the age of six years have almost twice as many behavior problems as non-allergic children. In 60 per cent of asthmatics emotional factors are important with reference to initiating or increasing the severity of the attacks.

In another general discussion of the allergic child Pounders[60] gives the impression that colic is generally of allergic origin. He also states that he has also seen at least two near deaths from penicillin and believes it a good policy to skin test patients before giving this preparation. (The reviewer notes that it is not stated whether the reactions were from crystalline penicillin in aqueous or saline solution or from some other type of penicillin preparation.)

Low grade fever may be due to allergy. The disappointing effect of change in climate is mentioned. Pounders states that other things being equal there is apt to be less trouble in a dry, warm, even tempered climate where high winds do not prevail and the pollen content of the air is low.

As regards the controversial problem of marriage between allergic individuals, Pounders states that it is a mistake for a physician to tell anyone not to marry; not to marry a certain individual; or not to have children. The physician is obligated, however, to explain the probable consequences of heredity with regard to certain diseases including allergy. When one parent is allergic, and the other is entirely free from trouble, 50 per cent of the children will probably show evidence of it but not necessarily as a major health problem. If both parents are affected, the probabilities are that three out of four of the children will develop allergic problems during the first ten years of life and this is apt to be a major health problem. If neither parent has any hereditary taint, then probably none of the children will be affected. This is quoted from Spain and Cooke.[74]

Clarke,[18] who has studied the subject of neuroallergy in childhood more extensively than anyone else, has presented a valuable review of this subject. Most of his work in this field was summarized in 1945.[31]

Franconi, Botsztejn, and Schenker[28] have contributed a long study of fifty-nine cases of anaphylactic reaction to mercury following the application of mercury ointment and the internal administration of calomel.

The annual review of Unger and Gordon[79] on bronchial asthma, as usual, is very complete and the editorial comments most instructive. The proceedings of the round table on asthma in children under the chairmanship of Smyth[72] present a very practical review of present-day methods of treatment.

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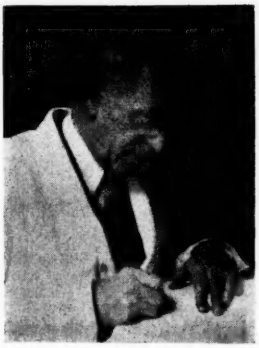
300 South Goodman Street

IN MEMORIAM

WILLIAM ATWOOD MOWRY, M.D., F.A.C.A.



Bill Mowry, as he was affectionately known among his friends, died rather suddenly at his home in Madison, Wisconsin, January 8, 1949.

Doctor Mowry was born June 2, 1880, in Geneseo, Illinois. In 1897 he graduated from Geneseo High School and in 1910 he graduated from Northwestern University Medical School. Following his graduation he served his internship at St. Luke's Hospital in Chicago, Illinois. From 1911-1921 Dr. Mowry was the physician at French Lick Springs Hotel in French Lick, Indiana. In 1923 he did postgraduate work for about a year at Bradley Hospital, University of Wisconsin. He also had postgraduate training in allergy at Richmond, Virginia, under the late Dr. Warren Vaughn. At the time of his death he was Clinical Professor of Medicine at the University of Wisconsin, an office which he had held since 1933.

Doctor Mowry has had a well-established practice which began twenty-five years ago. He was Head of the Allergy Department, State of Wisconsin General Hospital (University Hospital), and was on the staff of the Student Health Department of the University of Wisconsin. He was certified by the Board of Internal Medicine in 1937. Doctor Mowry was a member of the Dane County Medical Society, the Wisconsin State Medical Society, the American Medical Association, the Chicago Society of Allergy, the International Correspondence Club of Allergy, the American Academy of Allergy, the American College of Allergists and the Wisconsin Heart Association.

A consciencious and able teacher, Dr. Mowry had a very pleasing personality and made friends and won the respect of all who knew him. He was very active in the College affairs and at one time was chairman of the Educational Committee.

He is survived by his wife, Guinevieve, and one son, William A., Jr. The College will feel his loss. The members extend their sincere sympathy to Mrs. Mowry and her son.

GEORGE CHAMBERS ANGLIN, M.D., F.A.C.A.

Dr. George Chambers Anglin, one of the Canadian Fellows of the American College of Allergists, died April 14, 1948, at Toronto, as a result of a coronary thrombosis.

Doctor Anglin was born January 29, 1890, in Cork, Ireland. He attended the Royal University of Ireland and then the University of Toronto where he graduated in 1914. He served his internship at Toronto Hospital, Weston, Ontario, and did postgraduate work at London Hospital, Hopital de la Charite, and the University of Vienna. While doing postgraduate work he joined the Royal Army Medical Corps for three years. Doctor Anglin taught at the University of Toronto and the Toronto Western Hospital. At one time he was in charge of the Allergy Clinic for the Department of Veteran's Affairs with headquarters in Toronto. He was the consultant for diseases of the chest and allergy. Doctor Anglin was a staff member of the Toronto Western Hospital and Christie Street Hospital. He belonged to the Laennec Society, the Canadian Tuberculosis Association, the American College of

Chest Physicians, the Canadian Allergy Society and the American College of Allergists. He was also a diplomate of the American Board of Internal Medicine.

Doctor Anglin is survived by his wife, Ruth, two sons and two daughters. He was a tireless worker and was greatly esteemed by physicians and patients alike. Members of the College mourn his loss deeply.

PHILIP J. JORDAN, M.D., F.A.C.A.

Friends were shocked to learn of the sudden death of Dr. Philip J. Jordan who was stricken rather suddenly on August 31, 1948 at his home in San Jose, California.

Doctor Jordan was only thirty-seven years old at the time of his death. He was born April 15, 1911, in San Jose. After his graduation from San Jose High School, Dr. Jordan went to Stanford University where he received his A.B. in 1934. After four years at Stanford Medical School he served his internship at Mercy Hospital in Chicago. He was a resident at the Illinois Eye and Ear Infirmary during the years 1938-1942. Doctor Jordan served as a first Lieutenant of the United States Army Medical Corps during the last war. He passed his American Board Examination in 1942. At the time of his death he was teaching in the Nursing School, Santa Clara County Hospital and the Nursing School, O'Connor Sanitarium. He was preparing a paper entitled "Fibroma of the Limbus."

Doctor Jordan was very popular with his close medical associates, as well as with his patients. He was a member of the American Medical Association, the California Medical Association, the Santa Clara County Medical Society, the Pacific Coast Oto-ophthalmological Society, the San Francisco Ophthalmological Round Table, the American Academy of Ophthalmology and Otolaryngology, and the American College of Allergists.

Surviving are his wife, Bette Ann, and twin daughters, Sharon Lee and Chandelle Ann, and his parents, Dr. and Mrs. Peter A. Jordan. Members of the College extend their sincere sympathy to his family. They will feel his loss greatly.

SPONTANEOUS RIB FRACTURE IN BRONCHIAL ASTHMA

(Continued from Page 218)

SUMMARY

1. The case report of a patient with bronchial asthma who spontaneously fractured his eighth, ninth, and tenth ribs during paroxysms of cough is added to the literature.

2. The theories of the probable cause of such fractures are reviewed.

60 Gramercy Park

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News Items

THE NEW YORK ALLERGY SOCIETY

The New York Allergy Society will hold a meeting, Wednesday, May 4, at the New York Academy of Medicine, Room 440. The program will be announced later.

RESEARCH GRANTS

The sum of $500.00 has been granted by Marcelle Cosmetics, Inc., to the Division of Allergy, Montefiore Hospital, Pittsburgh, Pennsylvania, for research purposes.

Marcelle Cosmetics, Inc., has made a grant of $500.00 to the Division of Allergy at Tulane University. The money is to be used for the purchase of equipment for investigating problems in allergy.

SOUTHEASTERN ALLERGY ASSOCIATION

The Southeastern Allergy Association held its annual meeting at the Washington-Duke Hotel, Durham, North Carolina, January 22 and 23, 1949.

Dr. Oscar Swineford, Jr., University of Virginia, Medical College, Charlottesville, Virginia, was elected president. Dr. Oscar Hansen-Pruss, Duke University, School of Medicine, Durham, North Carolina, was elected vice-president. Dr. Katharine Baylis MacInnis, Columbia, South Carolina, was re-elected secretary and treasurer. Dr. Lewis D. Hoppe, Atlanta, Georgia, and Dr. Frederick Hieber, St. Petersburg, Florida, were elected executive committeemen at large.

The 1950 meeting will be held in Columbia, South Carolina, the exact date to be announced.

HUNGARIAN SECTION OF ALLERGISTS

The Hungarian Medical Trade Union Association of Physicians, Section of Allergists, held a meeting on December 15, 1948. In several lectures various speakers reported on their researches with Resactor, an extract of the embryonal liver tissue, known to be an activator of the reticulo-endothelial system and to produce phagocytosis.

Doctors Fekete, Plank and Francia-Kiss reported on the dermatological experiments with Resactor. Doctor Filipp reported on the effect of Resactor on the reticulo-endothelial system as controlled with an India ink histamine-storage method. Doctors Mathe, Filipp, and Matko reported their investigations of thirty-two anaphylactic dogs regarding changes in the heart, by demonstrating illustrative slides. Discussion: Doctor Pollitzer discussed his use of Resactor in the differentiation of various cases of hepatitis.

The questions of anaphylactic and allergic heart disturbances were discussed by Drs. M. K. Hajos, Mosonyi, Zarday, and K. Hajos, and special attention was called to the significance of clinical and experimental work in the evaluation of allergic heart diseases.

POSTGRADUATE CENTER FOR PSYCHOTHERAPY, INC.

The Postgraduate Center for Psychotherapy, Inc., the training associate of the Institute for Research in Psychotherapy, Inc., has been granted a provisional charter from the Board of Regents of the New York State Educational Department. It offers intensive training for psychiatrists in psychotherapy, leading to certification; also individual courses for general practitioners and non-psychiatric medical specialists in psychotherapy and psychosomatic medicine.

Clinical psychologists and psychiatric case workers are trained in methods that are within the scope of their education and skills, and which can contribute to an integrated program.

Both required and optional lecture courses are offered. Courses include the principles and practice of psychotherapy; psychodynamics and psychopathology; short-term psychotherapy utilizing psychobiological and psychoanalytical approaches; hypnotherapy; narcosynthesis; shock therapy; group therapy; case work therapy; psychological counseling; child and adolescent psychotherapy; case conferences and seminars; organization and operation of a community psychiatric clinic; projective techniques in psychotherapy; seminar on psychosomatic medicine; therapy of the neuroses and psychoses; compensation and medicolegal problems in psychiatry; anthropological and sociological aspects of psychiatry; and industrial psychiatry.

The Institute is in close co-operation with the Postgraduate Center and will also carry on a therapeutic, research and educational program.

Further information on this program may be obtained by writing to Stephen P. Jewett, M.D., Dean, or to Miss Janice Hatcher, Registrar, Postgraduate Center for Psychotherapy, Inc., 218 East 70th Street, New York 21, New York.

FORUM ON ALLERGY

The Pennsylvania Allergy Association and the Lehigh County Medical Society held a meeting at Allentown Hospital Nurses College on Wednesday, April 6, 1949. The following program was presented:

1:25 p.m. Welcome—ROWLAND W. BACHMAN, M.D.
President, Lehigh County Medical Society

1:30 p.m. "The Role of Fungi in Allergy"
JOSEPH W. PIEKARSKI, M.D.

2:00 p.m. "Problems in the Diagnosis and Management of the Allergic Nose"
CALVIN C. FOX, M.D.

2:30 p.m. "The Treatment of Bronchial Asthma"
WILL COOK SPAIN, M.D.

Intermission

3:20 p.m. "Food Allergy"
LOUIS TUFT, M.D.

3:50 p.m. "Antihistaminics—Uses and Abuses"
CHARLES M. BANCROFT, M.D.

4:20 p.m. "The Psychosomatic Aspects of Certain Allergic Disorders"
EDWARD WEISS, M.D.

Discussion after each paper.

GENERAL NEWS

Dr. Arthur F. Coca announces the opening of his office at 708 Park Avenue, New York, for the practice of pulse-dietary diagnosis as applied particularly in allergic diseases of internal medicine.

* * *

A graduate of the Marquette School of Medicine 1936, with one year's internship at the Sacred Heart Hospital, Spokane, Washington, a general rural practice from 1937 to 1942 in Ritzville, Washington, in the Army Medical Corp from 1942 to 1945, and now doing general work and study mostly limited to medicine, is desirous of graduate work and a residency in allergy. Communications should be addressed to the Secretary, American College of Allergists, 423 La Salle Medical Building, Minneapolis 2, Minnesota.

BOOK REVIEWS

HISTAMINE AND ANAPHYLAXIS and Their Relation to the Pathogenesis of the Science of Allergy. By M. Rocha E. Silva, Biological Institute of Sao Paulo, Brazil. 340 pages, 10 chapters, 65 illustrations, 4 colored illustrations. Price Cr $70.00, bound Cr $90.00. Sao Paulo: Grafica e Editora EDIGRAF Ltda., 1948.

Histamine, the normal cellular constituent, is discussed here in its entirety—its pharmacological make-up, manner of release, and consequent manifestations. The author has collaborated with prominent allergists in preparing the book, and much of the experimental work was carried out in the laboratories of Northwestern University of Chicago, the Mayo Foundation Institute of Experimental Medicine, and the Rockefeller Institute of New York.

The book contains a wealth of experimental data on the pathogenesis of the science of allergy and provides an intelligent approach to that most interesting of biological phenomenon: anaphylaxis. The growing importance of idiosyncrasy-manifestations (arsenicals, sulfas and their derivatives, penicillin, et cetera) is fully discussed as well as antihistaminic drugs and therapy related to the treatment of these manifestations. The paper stock and print are good. The diagrams and sketches are profuse and used intelligently. The book is written in Portuguese.

PRACTICE OF ALLERGY. By Warren T. Vaughn, M.D., Second edition, revised by J. Harvey Black, M.D. 1132 pages (69 chapters; 16 parts). 333 figures. Price, $15.00. St. Louis: C. V. Mosby Co., 1948.

The first edition of this volume by Dr. Vaughan was one of the most popular textbooks on allergy during his time. The book was characterized by its completeness in appearance, reflecting the personality of a man of exceptional ability in the field of research and clinical analysis. Most of the book represented his own clinical experiences. Its details made it invaluable to the specialist in allergy as well as the student. Impartial credit was always given to other contributors in discussing any phase of the subject.

With the appearance of the revised edition by Dr. Black, the new volume has become one of the most complete practical text-books on allergy today. Dr. Black is well known for his pioneer work and contributions to the literature in allergy. As a man of fair judgment when evaluating and presenting the more recent developments in investigative and clinical allergy, he is particularly fitted to make the valuable revision and additions to this second volume.

The bibliography has been considerably enhanced. The paper stock, illustrations and binding merit mention of the publishers.

ALLERGY TO COTTONSEED AND OTHER OILSEEDS: Excerpts from Testimony before the Administrator, Federal Security Agency in the matter of fixing and establishing definitions and standards of identity for mayonnaise, French dressing, and related salad dressings (Docket FDC-51). Public hearings held at Washington, D. C., November 18, 1947 and January 6 to 8, 1948. National Cottonseed Products Association, Inc., Memphis, Tennessee. (Not available for purchase or general distribution, but is loaned by physicians or scientists interested from the medical or scientific standpoint.)

This publication is issued as a contribution to the literature of allergy. It is well known among allergists in particular, that cottonseed protein is a relatively frequent offender in producing allergic symptoms such as bronchial asthma. This holds true of the inhalation of other proteins from seed dusts such as soya bean, castor bean, or coffee bean and others. Industrial mills grinding these seeds for various purposes will produce a certain amount of concentrated seed dust in the adjacent atmosphere and people with allergic tendencies may acquire sensitivity to these dusts through inhalation so that they develop asthma or other allergic manifestations. These same

people develop allergic symptoms upon eating seeds such as soybeans, coffee, et cetera. It was natural for allergists, therefore, to incriminate the edible oils made from seeds, such as cottonseed oil. The latter is universally used in salad dressings such as mayonnaise. However, as closer studies were made by authoritative allergists interested in the subject, it became evident that proof was lacking that the pure oil of these edible seeds, such as cottonseed oil, produced any allergic symptoms in patients sensitive to cottonseed protein. Since the question of cottonseed oil remained controversial, and under the terms of the Food, Drug, and Cosmetic Act the labels for mayonnaise, French dressing, and related salad dressings, specific naming of the vegetable oils contained in them has not been required, the term "Vegetable Oil" has been accepted as permissible when declaring these ingredients.

"The chief purpose of this hearing was to compile, for consideration of the Administrator, a record of the testimony of expert witnesses who were called to develop information pertaining to the composition, quality, and kinds of ingredients and to the labeling of optional ingredients. Based upon consideration of the evidence presented at this hearing, the Administrator will issue an official regulation when fixing standards of identity of the foods under consideration."

This volume contains the testimony of six expert witnesses on allergy to cottonseed oil and other oilseed products, and two expert witnesses "concerning relevant factors of vegetable oil technocology." This hearing was authorized by the Federal Food, Drug, and Cosmetic Act and held before the Administrator, Federal Security Agency.

The sum and substance of this testimony furnishes convincing evidence that cottonseed oil sensitivity does not exist or if it does exist, that it is extremely rare. Since cottonseed protein is a very potent allergen in a certain percentage of allergic patients, it would appear to the reviewer that those cases which appear to be sensitive to the vegetable oils are, in all probability, sensitive to an impure oil or one contaminated with the protein fraction of the seed and then the patient would have to be one of those who is extremely sensitive to cottonseed protein and who also manifested sensitivity on clinical trial to cottonseed protein.

AN EXPERIMENTAL STUDY OF THE EFFECT OF ALCOHOL AND ALCOHOLIC BEVERAGES ON ALLERGIC REACTIONS

(Continued from Page 194)

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